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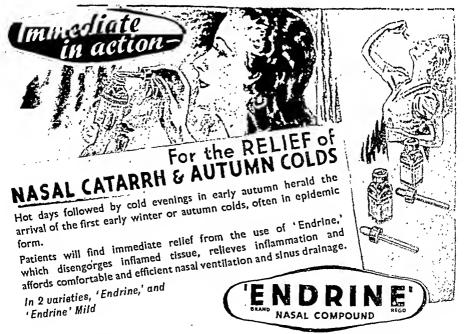
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THE BASIS OF PENICILLIN THERAPY *

By T. J. MACKIE, C.B.E., M.D.

Professor of Bacteriology, Edinburgh University

THE discovery of substances combining high anti-microbial potency with non-toxicity to the tissues has been a primary object of all chemotherapeutic research. In the early years of this century Ehrlich's great work on the chemotherapy of trypanosome and spirochætal infections, and subsequently, studies of the antiseptic dyes seemed to bring this within the range of practical possibilities. More recently the sulphonamide compounds have provided a still closer approach. That very fortunate observation by Fleming of the lytic action of the mould, *Penicillium notatum*, towards a staphylococcal culture, and his resultant discovery of penicillin have practically attained, in respect of several bacterial diseases, the objective research workers in the field of chemotherapy have long striven for.

Though at one time it was thought that this objective might be reached along rational lines of combined chemical, bacteriological and experimental studies, the long-sought-for substance came to light in an entirely different way, and penicillin has been successfully used as a therapeutic agent without knowledge of its chemical structure or its chemical relationships to other antiseptics. But we know that it is only one product among many of a similar category. Years ago it was shown that in the general struggle for existence in nature one micro-organism might be antagonistic to another—the phenomenon being described as antibiosis; and it is now appreciated that such antibiotic action in general is due to chemical substances which, produced by one species, kill or inhibit the growth of another. In the last few years the study of this subject has been most progressive, and a large number of antibiotic agents derived from moulds, algæ, bacteria and even the higher plants have been demonstrated and in some cases chemically defined, while their antagonism to various pathogenic bacteria has been carefully evaluated both *in vivo* and *in vitro*, and their toxicity to the tissues has also been estimated. It is of some philosophic interest that those which are antagonistic to pathogenic bacteria have been derived mainly from soil organisms—' fungi, actinomycetes and aerobic sporing bacilli.

So far penicillin remains unsurpassed as the antibiotic of choice for practical chemotherapy, but of course its limitations as well as its virtues must be appreciated.

Studies of antibiotics have shown that they are not unselective in their action on different bacterial species, and this is very true of penicillin. While most Gram-positive pathogenic bacteria are highly sensitive to it, Gram-negative organisms, with the striking exception of the gonococcus and meningococcus, are relatively insusceptible, and the same applies unfortunately to the tubercle bacillus. It is of special biological interest and practical importance that spirochætes are susceptible, while viruses, pathogenic fungi and protozoa are not so. However, a wide range of pathogens are sensitive, and thus a considerable number of bacterial infections are amenable to penicillin therapy.

While penicillin and certain other antibiotics are inactive or only weakly active towards such Gram-negative organisms as *B. coli*, the typhoid bacillus, the dysentery bacilli, etc., substances of the same category have been discovered possessing this property which penicillin lacks, and it is perhaps a justifiable speculation that in the course of time from among these antibiotics or chemically related compounds may be built up a complete armamentarium of therapeutic agents for all bacterial diseases, including tuberculosis. But again we must bear in mind the limiting factors. Thus, " tyroeidin," an antibiotic derived from *B. brevis*, is active against both Gram-positive and Gram-negative organisms, but it is toxic and not effective *in vivo* (see Waksman, 1941). " Clavacin " from *Aspergillus clavatus*, probably the same as the antibiotic named " patulin," is also active towards both Gram-positive and Gram-negative bacteria, but is highly toxic to animals (see Katzman *et al.*, 1944). Even individual strains of known sensitive organisms may be resistant to penicillin, and the proportion of such strains in a species may possibly increase as the substance becomes extensively used for treatment of prevalent diseases. This has already been suggested from experiences with the sulphonamides. Sensitivity, moreover, is not necessarily a fixed property of a strain and the possibility of an organism becoming penicillin-fast *in vivo* has to be considered. For example, Schmidt and Sesler (1943) have demonstrated resistance acquired by a pneumococcus under the influence of penicillin in experimental animals.

Following Fleming's discovery of penicillin (Fleming, 1929) and his demonstration of its remarkable properties, there was a long delay in applying it in actual therapy. This was due to the peculiar difficulties encountered in producing penicillin in quantity, extracting it from cultures, concentrating and purifying it. The first advance was made by Clutterbuck, Lovell and Raistrick (1932) who grew *Penicillium notatum* on a " synthetic " medium (Czapek-Dox medium) containing certain inorganic salts and glucose. The expectation was that a simple medium of this type, as compared with media of complex chemical composition, would facilitate the isolation of the active principle in a

pure state ; but when the ordinary methods of concentrating it from the culture fluid were adopted, the active substance was rendered inert. However, partial success was attained by ether-extraction of the acidified fluid ; but again an obstacle was encountered, since the evaporation of the ether even at low temperature led to considerable inactivation. It was not till 1941 that a practicable method of producing purified penicillin for therapeutic use was reported ; this success was achieved by Florey and his co-workers at Oxford University (see Abraham et al., 1941 ; and Abraham and Chain, 1942). I will not enter into details except to say that the process involved cultivation of the mould on the synthetic medium referred to above (with yeast extract added), acidification of the culture fluid, extraction with an organic solvent (amyl acetate), the ultimate formation of the sodium or calcium salt of penicillin (which is of the nature of an organic acid), and lyophilic drying to render the substance in the form of the water-soluble yellowish-brown powder with which we are now familiar. The great instability of penicillin was, of course, one of the outstanding obstacles in all this work ; but a fundamental difficulty in the production of the substance for therapeutic purposes was the small amount of it in cultures of the mould. This necessitated very large-scale cultivation of P. notatum on the surface of fluid medium (the mould being a strict aerobe), and even a great bulk of culture yielded only a small quantity of penicillin. It was clear that if manufacture was to be facilitated, greatly improved methods of cultivation would be required.

In 1940-41 a systematic bacteriological study of wounds was being carried out in Edinburgh by Dr H. L. de Waal ; this included a clinical and bacteriological evaluation of the various antiseptics in common use at the time (see de Waal, 1943). Penicillin was already being produced and studied by the Oxford workers but was not available to others at this stage. Dr de Waal and Mrs Jean MacNaughtan, following the methods of the Oxford workers, prepared a small amount for local application to wounds and burns, and a few cases were so treated. De Waal formed the impression that it was superior to other antiseptics in controlling certain types of wound infection, but his work was discontinued on his entering the army. Later it was decided to produce purified penicillin on a large scale for therapeutic trials in Edinburgh, including systemic administration, and Dr S. W. Challinor and Mrs MacNaughtan undertook the difficult technical work of production. Professor Learmonth gave us his full support and the co-operation of his University department, and the University Court voted a sum of £1000 to cover the additional expenses. I would like to take this opportunity of acknowledging the assistance and encouragement given by the University Court to this early venture in penicillin therapy in Edinburgh.

The fundamental difficulty at that time in penicillin production—already referred to—so impressed my colleagues that they decided, while engaged in production by the then accepted method, to devote their attention to improved procedures, and they devised a method

which increased the yield threefold (Challinor, 1942; Challinor and MacNaughtan, 1943). Later we were informed of a greatly improved method introduced in the United States involving the incorporation in the culture medium of corn-steep liquor (Clifton, 1943), which enhanced the yield to a very high degree. This method was successfully applied in Edinburgh. Corn-steep is a by-product in the manufacture of starch and possibly acts by supplying some unknown factor necessary for the synthetic metabolism of the mould. Improved methods of extraction, of which we had confidential information from other sources, were studied, and a new process for concentrating penicillin (freezing and fractional thawing) was also devised by Challinor and MacNaughtan (1945). In the lyophilic drying we had the assistance of the Edinburgh Blood Transfusion Organisation with its plasma-drying plant.

The result of the Edinburgh work was a highly purified product equal to the best of those now in use and suitable for any form of parenteral injection. It will be understood that our production was still on a very small scale as compared with factory output which was beginning in 1943, and when the Medical Research Council were able to give Professor Learmonth an allocation from their supplies for clinical trials in Edinburgh, our production was discontinued in favour of other lines of research. Since that time still further progress has been made in large-scale manufacture, especially in the United States, e.g. by a process in which the mould is grown in a large bulk of aerated culture medium in place of the earlier surface cultivation. The work on production in Edinburgh certainly gave us a very close insight into the peculiarities of this new remedy, and I would now make some reference to these.

As mentioned, it was early recognised that penicillin behaves as an acid, forming water-soluble sodium and calcium salts, in which form it is used for treatment. The products at present supplied in the form of a yellowish-brown powder are far from chemical purity —at most only one-third pure. In fact, the colour is due to impurities, namely the pigments of the mould. Though pyrogenic impurities may be present and their effects may be observed clinically, the whole product in the doses used is practically non-toxic, and relatively large quantities can be introduced into the body. Of course by animal experiment it has been shown that penicillin, as prepared at present, is not altogether devoid of toxicity, but there are also indications that this toxicity may be largely due to impurities—the purer the product the less toxic it is (see Hamre et al., 1943). In any case lethal doses ascertained in small animals in terms of body weight are far in excess of those employed for therapy in man.

As regards the chemical constitution of penicillin, it has been recognised to be an organic acid with nitrogen and sulphur in its molecule. Since it has now been obtained in pure crystalline form its empirical formula and chemical structure may be known to those concerned with its chemical study; but the facts have not been

disclosed,* and its synthesis and the practicability of this have not been reported. Presumably penicillin will continue to be made by the biological process of growing *P. notatum* in laboratory culture, and extracting the active principle from the culture fluid.

The instability of penicillin, especially in watery solution, has been one of its special features and an awkward one in production and clinical use. For this reason it has been insisted that solutions should be freshly prepared for treatment and kept at a low temperature. Penicillin is easily inactivated by acids, alkalis, alcohol and a variety of other chemicals. It is also relatively thermolabile and cannot be subjected to heat sterilisation ; it can be sterilised, where necessary, by filtration of the solution through a Seitz asbestos filter. In the form of the desiccated powder its stability is much greater, but even so it cannot be handled like ordinary therapeutic chemicals, and to maintain its potency over the longest period it should be kept in a refrigerator in properly sealed bottles or ampoules. The sodium salt is also subject to the drawback of being deliquescent in air.

Thus, penicillin must be handled by a special technique and not by the simple measures applicable to the stable substances that are being generally dispensed for medical use. When it goes on the market and is in common use, one foresees possibilities of failures due to improper handling ; this must be obviated by appropriate measures. On the other hand, improved stability may be associated with the more refined preparations now available. Thus Kirby (1944*a*) has shown that sodium-penicillin from eight different American manufacturers in weak solution need not be refrigerated during one or two days after preparation, and has stated that no deterioration may occur even within seven days at room temperature. Our own experience has been that some degree of deterioration results on keeping solutions at room temperature, but preparations vary in this respect.

Penicillin is also readily destroyed by certain enzymes, *e.g.* takadiastase (Lawrence, 1943), and it is also of the greatest biological interest that various bacteria which are insensitive to penicillin produce substances, probably enzymic, which inactivate penicillin. A diffusible product of this nature, called penicillinase, has been specially studied, and penicillinase-producing organisms seem to belong to two main groups, the aerobic sporing bacilli (e.g. *B. subtilis*) and the aerobic non-sporing Gram-negative bacilli (e.g. *B. coli*) (Bondi and Deitz, 1944). It is of practical importance that contamination of a penicillin solution by one of these organisms may reduce or annul its activity, and the same effect may occur in a wound or suppurative lesion infected by such organisms, e.g. *B. pyocyaneus*, so that even a sensitive organism present, such as *Streptococcus pyogenes*, may be unaffected by penicillin introduced into the lesion. While an organism producing penicillinase would not be susceptible to penicillin, penicillin-resistance is not in all cases due to the production of this substance, and the acquisition of resistance cannot be correlated with the acquired production of

* Published since this paper was written (*Nature*, 1945, 156, 766).

the enzyme (Bondi and Dietz, 1944). Thus Kirby (1944b) has isolated from certain naturally resistant staphylococci an intracellular, non-diffusible inactivating substance. The various bacterial products which destroy penicillin require further study, from which might emerge significant information on the whole question of sensitivity and resistance.

The instability of penicillin in the presence of acid and certain enzymes, and the likelihood of its being inactivated by intestinal bacteria, has seemed to contra-indicate its oral or rectal administration, though, as shown by Chain et al. (1940) it can be absorbed from intestine. Thus, up to the present, the accepted mode of administration has been parenteral. Penicillin, however, is not inactivated by saliva, pepsin, bile, or succus entericus, and inactivation by gastric juice is proportional to its acidity (Rammelkamp and Keefer, 1943; and Rammelkamp and Helm, 1943). Little and Lumb (1945) have opened up the question of oral administration as a practical procedure. They argue that penicillin undergoes a stabilising change during passage through the body and that admixture with raw egg has such stabilising effect; they have administered penicillin in egg by the mouth after a dose of alkali and claim that a satisfactory bacteriostatic level is attained in the blood. Heatley (1945) has not been able to confirm fully these findings and points out that the effective oral dose would be at least three-fold that by injection. The whole question of oral versus parenteral administration is another matter for further investigation, and of course now that penicillin is being produced in large quantity the difference in the effective dose may not be a serious disadvantage to oral administration. The general value of penicillin would be greatly enhanced if it could be administered orally like the sulphonamides.

The remarkable quantitative potency of penicillin was appreciated by the earlier workers; thus, it was found that in vitro a purified preparation could prevent the growth of staphylococci, at a dilution of 1 in 50,000,000. This high potency and its relative non-toxicity in fact determined the choice of penicillin for the intensive study which has been given to it, and early work also showed that expectations from in vitro observations were not disappointed by experimental results in vivo. The fact that it is active in blood, serum, pus and inflammatory exudates, also seemed to confer on it a superiority over many other antiseptics. Further, it has been stated that it acts efficiently on large as well as on small numbers of bacteria (M.R.C. War Memo., 1944)—again unlike other antiseptics; but I will refer later to this question, as such statement now requires some qualification.

As penicillin is a biological product of unknown chemical structure* and an impure one, whose activity cannot be assayed by chemical means, it has been necessary to standardise preparations by a quantitative bacteriological test, and on this basis to recognise an

* See footnote on p. 5.

arbitrary unit for regulating dosage. The unit is the so-called Oxford Unit originally defined as that amount of penicillin which will just inhibit growth of a given strain of staphylococcus, when diluted with 50 ml. of meat-extract broth. It may now be defined as representing the antibacterial potency of a given weight of standard penicillin. (A million units are designated a mega unit.) 500 units may be contained in 1 mgm. of the powder supplied for therapeutic purposes. One mgm. of the perfectly dried crystalline sodium salt of penicillin would be equivalent to 1667 units (Dale, 1945).

Though Fleming originally pointed out that penicillin is a bacterio-lytic agent, in subsequent literature its growth-inhibitory properties were mainly referred to, and when it first became a therapeutic substance it was spoken of and thought of as bacteriostatic; in fact, the impression became general that it was similar in action to the sulphonamides which are solely bacteriostatic in the concentrations attained in the blood after oral administration. The aim in systemic penicillin therapy has therefore been to maintain in the blood, or at the locus of infection, a constant " bacteriostatic level." But here a difficulty was encountered: penicillin is rapidly absorbed after intramuscular or subcutaneous injection and also rapidly excreted in the urine. The maintenance of the bacteriostatic level was soon found to be impossible unless by frequently repeated injections, e.g. every three hours day and night, and when a case had to be treated over a long period, the difficulty was a serious one. It was overcome by the procedure of continuous administration, the " intramuscular drip " method now in common use. It should be mentioned that Edinburgh workers have done much to make this method a feasible and satisfactory one (McAdam, Duguid and Challinor, 1944).

To control or check the degree of activity of penicillin in the blood a bacteriostatic test was introduced. One of the first methods advocated for this purpose was to implant a very small inoculum of a standard staphylococcus in varying dilutions of patient's serum in slide-cells, incubate and observe the presence or absence of growth and the relative amounts of growth in terms of the number of colonies (M.R.C. War Memo., 1944). We found this technique unsatisfactory in certain respects and an alternative and simpler method was devised. This latter has now been very extensively applied for investigative purposes and for routine therapeutic control. It consists in determining in small tubes the inhibition of growth of a standard staphylococcus implanted in undiluted serum and a series of varying dilutions of serum *in broth*, from 1 in 2 to 1 in 16, growth being denoted by visible turbidity after twenty-four hours' incubation (checked if necessary by sub-inoculation on solid medium).

The question arose as to the bacteriostatic titre which should be aimed at. On rational grounds it seemed that if the staphylococcus completely failed to grow in the undiluted serum this should be considered adequate in the control of a blood infection. As McAdam, Duguid and Challinor have pointed out, under treatment by

intramuscular drip with 100,000 units per day, in the great majority of cases undiluted serum is completely inhibitory; some yield higher bacteriostatic titres; a fair proportion 1 in 2 or 1 in 4, and a few 1 in 8 or 1 in 16. It is difficult to explain the variation in titre on a standard continuous dosage; but varying absorption from the tissues or rate of excretion might account for individual differences. Clinical experience in Edinburgh has certainly indicated that if complete inhibition of growth occurs in undiluted serum, whether or not dilutions also give the same effect, satisfactory therapeutic results are obtained in such cases as acute staphylococcal osteomyelitis with blood infection. But this does not necessarily apply to all types of cases, and though this concentration of penicillin in the blood may suffice to control a blood infection by a highly susceptible organism, it may be inadequate for the treatment of an infective lesion in which organisms are present in very large number and are protected from the blood. Of course this difficulty is overcome in accessible lesions by direct local administration, and in some types of infection local administration is the only necessary mode of administration. The possibility of penicillin being partially inactivated in blood or serum *in vivo* and *in vitro* as Bigger (1944a) has pointed out, must also be borne in mind in gauging levels of penicillin concentration in the blood. In any case, where serum exerts an inactivating effect on penicillin, the titre in the bacteriostatic test will underestimate the concentration. The serum bacteriostatic test has its limitations, but it has proved invaluable in investigative work and provides a most useful check in routine therapy. The technique we have employed is essentially simple and can be applied to the titration of penicillin in cerebrospinal fluid, urine, serous and purulent exudates, the range of dilution being extended where necessary.

In selecting cases for penicillin therapy it is essential to ascertain, by thorough bacteriological examination, the causative organism or organisms. If these are known insensitive species, penicillin treatment would not of course be indicated. The question also arises of the sensitivity of a particular strain of a known sensitive species; thus, in wounds not all staphylococci are sensitive and failure to respond might be due to this. The possibility of a sensitive strain becoming less sensitive during prolonged treatment has also to be considered. A test for sensitivity is therefore an essential laboratory method ancillary to practical therapy. This has usually been done by a technique originally advocated by Fleming in which a " gutter " is cut out of an agar or blood-agar plate and penicillin introduced into it so that it diffuses into the medium, its degree of concentration depending on proximity to the gutter; stroke cultures are then made at right angles from the gutter. A sensitive organism shows cessation of growth within a certain distance from the gutter. The relative degree of sensitivity can be assessed by the distance from the gutter at which growth stops. While this test is useful and simple, it gives only a rough estimate. More accurate estimates can be obtained by

placing varying concentrations of penicillin in tubes of fluid medium, adding to each a given inoculum and determining the maximum concentration that prevents growth. Observations made in this way show that sensitivity or resistance is relative, though it has been customary to classify species as if these properties were absolute in all cases. Certain organisms exhibit a high degree of resistance, e.g. *B. pyocyaneus*, *B. coli*, *B. proteus*, *Salmonella* group, dysentery bacilli and *V. choleræ* (*B. pyocyaneus* being outstanding in this respect). *B. pestis*, *B. influenzæ*,* the *Brucella* group and enterococcus are generally classified as resistant, but their resistance is of a lower grade than that of *B. coli* and the *Salmonella* group. *Strep. pyogenes*, *Strep. viridans*, pneumococcus, *Staph. aureus*, *B. diphtheriæ*, *B. anthracis*, meningococcus and gonococcus are " sensitive " as compared with *B. coli* and the *Salmonella* group, being generally unable to grow in a concentration of 0·1 unit per c.c., but even among these sensitive organs there are quantitative differences ; thus, *Strep. pyogenes*, *Strep. viridans*, the pneumococcus, meningococcus and gonococcus are more sensitive usually than *Staph. aureus*, *B. diphtheriæ* and *B. anthracis*.

As I have mentioned, penicillin has been used therapeutically and its use has been regulated on the basis of its being purely bacteriostatic. While a bacteriostatic agent may be highly effective in many bacterial infections by controlling growth in the tissues and so assisting the natural defences, some of the spectacular and rapid results of penicillin treatment have seemed more compatible with actual bactericidal action. About a year ago we were so impressed with this that it was decided to investigate the question, and with Dr J. P. Duguid's collaboration a series of most interesting *in vitro* observations have been made on the mode of action of penicillin. In the first experiments penicillin in varying concentrations was added to broth and in parallel to Locke's salt solution ; varying concentrations of a standard *Staphylococcus aureus* culture were inoculated into these ; stroke sub-inoculations with a standard loop were then made on plates of solid medium (containing an appropriate amount of penicillinase) immediately on admixture of penicillin and culture and at intervals during incubation at 37° C. ; the plates were incubated and the resulting growths compared. It was thus possible to ascertain whether the effect of the penicillin was bacteriostatic or bactericidal, the degree and speed of the effect, its relationship to the phase of growth or vegetative activity of the organism, and the influence of bacterial numbers. In later experiments, by observing at intervals the degree of turbidity of the mixtures made in fluid medium, bacteriolysis if it occurred could also be determined.

The results demonstrated definite bactericidal and bacteriolytic effects when penicillin acted on the organisms *in a nutrient medium*, commencing after about five hours and progressing during twenty-four

* Recent evidence indicates that *B. influenzæ* type C is sensitive ; this is a common type in meningeal infections (Forgacs *et al.*, 1945, *Lancet*, 1, 785).

hours, *i.e.* the period when active growth occurred in the absence of penicillin. In the salt solution, in which the organisms merely survived without growing, there was no killing. These findings at once suggested that penicillin could only affect organisms in their active phase. This work has been extended along various lines and with different organisms and the results show that penicillin in " therapeutic " concentrations acts as a bactericidal agent and is not merely bacteriostatic like the sulphonamides. In fact, by the method used, the contrast between sulphanilamide and penicillin is striking, the former being

SERIES OF DECIMAL DILUTIONS OF ORGANISMS

	1	2	3	4	5	6	7	8	9	
SUBINOCULATION, IMMEDIATE										
1000 — AFTER 24 HRS.										BACTERICIDAL EFFECT ALMOST COMPLETE BACTERIOSTASIS
200 " "										
100 " "										}
20 " "										VARYING DEGREES
10 " " THERAPEUTIC LEVEL										OF PARTIAL
2 AFTER 24 HRS.										BACTERIOSTASIS.
1 " "										}
NO SULPHANILAMIDE " "										GROWTH WELL DEVELOPED IN BROTH.

SULPHANILAMIDE MG./100 c.c.

REPRESENTING COMPARATIVE AMOUNTS OF GROWTH FROM STROKE SUBINOCULATION ON PLATE WITH STANDARD LOOPFULL OF MIXTURE OF SULPHANILAMIDE AND ORGANISMS IN BROTH.

NO GROWTH

CHART 1.—Sulphanilamide and *Streptococcus pyogenes* in Broth.

only bacteriostatic in " therapeutic " concentrations and very dependent on the number of organisms with which it is brought into contact. As was pointed out by early workers on this subject, sulphanilamide is only effective on small bacterial inocula. It has been stated that penicillin acts alike on large and small numbers of organisms, but in our experiments this has not been so ; thus in the presence of a high bacterial concentration its effect may be annulled. Illustrative results of these experiments are shown graphically in Charts 1 and 2. Since we started these studies a number of papers have been published by others on the same subject, and all writers agree that penicillin is bactericidal and bacteriolytic and that these effects are dependent on,

and proportional to, the vital activity of the organism. According to Hobby and Dawson (1944) conditions which increase the rate of growth of bacteria increase the rate at which penicillin acts. Todd (1945) has fully demonstrated the lytic action of penicillin towards a variety of organisms and that this effect is most rapid when the organisms are at the maximal rate of growth.[*]

Thus an important principle has now been established : the more active the growth of a micro-organism the more susceptible it will be to penicillin ; and we can understand the remarkable results of

SERIES OF DECIMAL DILUTIONS OF ORGANISMS.

1   2   3   4   5   6

SUBINOCULATION, IMMEDIATE

PENICILLIN UNITS PER C.C.		
100·	AFTER 5 HRS. " 24 "	VARYING DEGREES OF BACTERICIDAL EFFECT.
1·	AFTER 5 HRS. " 24 "	
0·09 THERAPEUTIC LEVEL	AFTER 5 HRS. " 24 "	
0·05	AFTER 5 HRS. " 24 "	
0·01	AFTER 5 HRS. " 24 "	BACTERIOSTATIC EFFECT
No PENICILLIN	AFTER 5 HRS. " 24 "	GROWTH COMMENCING IN BROTH " WELL DEVELOPED "
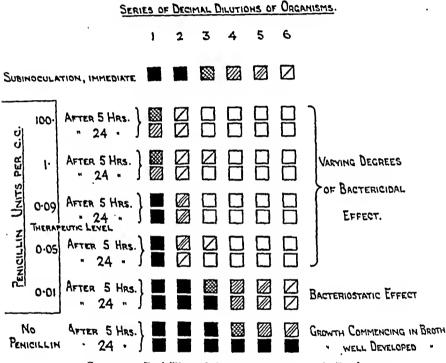
CHART 2.—Penicillin and *Streptococcus pyogenes* in Broth.

penicillin treatment in the most acute forms of infection. The full implications of this principle must also be considered. Our present methods of continuous administration, though logically the optimum if penicillin acted only as a bacteriostatic agent, may fall short of the true optimum. Thus intermittent dosage, the doses being suitably timed, might prove more effective than the continuous method. This has also been emphasised by Bigger (1944b), who points out that when large numbers of bacteria in the body are brought into contact with penicillin a certain proportion will be in the inactive phase at the time and these survive or persist ; later the survivors will become active and then susceptible to penicillin. It is unlikely that one large

[*] Todd (*Lancet*, 1945, 2, 172) now states that the most probable explanation of bacteriolysis produced by penicillin is that the organisms are first killed by penicillin and then autolysed.

dose would eliminate all organisms especially when these are very numerous ; some will survive as we see in laboratory tests, and repeated doses would usually be required for a final cure. The actual optimum dosage requires also further investigation in various types of infection.

How penicillin interferes with the vital chemical activity of bacteria, so leading to their death and disintegration, still presents an intriguing problem which can only be solved along biochemical lines, and a knowledge of the chemical structure of the substance is required for its elucidation. Whatever the chemical mechanism of penicillin action may be, it affects a metabolic function involved in the early stages of development (Chain and Duthie, 1945).

In building up our knowledge of how penicillin acts on bacteria, studies of morphological changes in bacterial cells under the influence of penicillin have been of some interest and possible significance. It had been pointed out in 1940 by Gardner that marked morphological alterations were produced by penicillin, and he stated that such effects occurred in higher dilutions than that causing inhibition of growth. He described elongation or spherical enlargement of the cells with imperfect fission. We have also carried out a series of observations on this aspect using for the purpose the microscope-incubator in which bacteria can be examined microscopically at any time during the whole course of their growth. The anthrax bacillus has been selected for these studies (though not exclusively) in virtue of its large size, its spore production and susceptibility to penicillin. Results depend on the amount of penicillin present, but in " therapeutic " concentrations the bacillary organism is seen to undergo enlargement, to lose its natural rectangular shape and become oval, spherical, or irregularly rounded ; finally, sudden disintegration occurs leaving behind only amorphous residue or a " ghost " cell. The early changes occur while multiplication and division are still proceeding. Bacterial cells in the resting phase in a non-nutrient medium show practically no change. High concentrations of penicillin may bring about lysis without prior enlargement (see Fig.). Spores, which are generally regarded as so highly resistant to most antiseptics, are very susceptible to penicillin provided they are present in a nutrient medium ; the initial stage of germination is first observed and then, according to the amount of penicillin, either great enlargement, like that of the vegetative form, followed by rapid disintegration, or lysis without prior enlargement. These findings are of practical importance in the use of penicillin as a prophylactic against gas-gangrene where the organisms are implanted in the tissues in the spore form. An important principle in regard to the destruction of spores is that they must first commence to germinate ; spores remaining in the resting phase in a non-nutrient medium are unaffected. This principle may also have applications to other antiseptics.

The observations described above must at present be interpreted with some reserve, since the morphological changes and also the final

lysis represent only secondary phenomena in the action of penicillin on the bacterial cell.

Such then in brief is our basic knowledge of penicillin as a therapeutic agent. Its great value in various bacterial diseases has

The Effect of Penicillin on Growing Anthrax Bacilli.
(*From drawings by Dr J. P. Duguid*)

now been established beyond any doubt; the exact scientific proof of its therapeutic superiority over other methods of treatment, while also accepted in certain diseases on the available clinical data, in general remains to be proved by controlled comparative trials on a sufficiently extensive scale, and such trials present great difficulty in their proper execution. When penicillin fails in conditions in which on rational grounds it might be expected to succeed, we have still

incomplete knowledge of the limiting factors. There is also scope for further study of optimum dosage and mode of administration. It can only be through a full knowledge of the basis of penicillin therapy that optimal methods will be attained and we are still at the stage of learning the fundamental facts. In the laboratory we have certainly gained a vivid impression of the remarkable properties of penicillin and its superiority *in vitro* over the sulphonamides in respect of certain bacteria, and we can now understand its almost dramatic effects in the most acute infections ; we can also appreciate its limitations.

The problem of the chemistry of penicillin and its chemical action is of fundamental importance, for as I have stressed, penicillin is only one of a group of analogous or related substances, and within this group may be found agents which will achieve therapeutic effects where penicillin fails. In fact, penicillin has a far-reaching significance in medicine and biology, but this at present is difficult to assess. Here is our wider problem and our greater hope.

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THE CLINICAL USE OF PENICILLIN *

By J. R. LEARMONTH, Ch.M., F.R.C.S.Ed.
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WHEN I was honoured by being asked to give this lecture, I protested that it should be a symposium. Unfortunately this is not possible under the conditions of the Honyman Gillespie Trust, and to-day I appear as spokesman for a team of clinical workers who have given much time and much thought to the problem of penicillin treatment ever since its therapeutic possibilities were introduced to the profession by Florey and his colleagues, whose brilliant and laborious work put to practical use the original fascinating observation by Fleming. In the early days Dr McAdam and Mr Aird were most immediately concerned, and later they were joined by Dr McCall ; but other clinical colleagues have co-operated most willingly, as have also the administrative staffs of the various hospitals in Edinburgh. The work has been done in close co-operation with Professor Mackie and his younger colleagues ; important as was this co-operation in the early phases, I emphasise that it must continue if penicillin therapy is to be effective and productive of information on which subsequent progress can be based. So short a lecture must be almost wholly limited to practice and impressions in Edinburgh, and I have excluded the many valuable applications of penicillin to the problems of war surgery. It is impossible to deal with the vast literature on penicillin which has already accumulated, to which at almost every turn we have been greatly indebted ; moreover, this lecture is designedly a simple one, intended for those who have little or no experience in the use of penicillin rather than for those who have had considerable experience. For the purpose of the lecture I have made free use of comments from colleagues, to whom I am greatly indebted ; reference will be made to them at appropriate times, and no doubt they will be publishing their individual experience in detail in suitable journals.

The story of the use of penicillin in Edinburgh may be divided into three periods. Originally, through the kindness of the University Court which I take this opportunity of acknowledging, it was possible for the Department of Bacteriology to make a small quantity of penicillin in my Department, mainly from a culture kindly supplied by Dr R. D. Coghill, of the United States, and also by Dr J. W. Trevan, of the Wellcome Physiological Research Laboratories. The limited amount available restricted its clinical application, but the solution of certain interesting problems in its preparation and concentration— as they existed at that time—were advanced by the work of Professor Mackie and his team. During the second period I had the privilege

of receiving small supplies from the Penicillin Clinical Trials Committee
of the Medical Research Council. These were intended for purposes
of research, particularly in cases of acute osteomyelitis.   During this
period every patient except two was hospitalised in the Royal Infirmary
or other general hospital, irrespective of social position.   The two
exceptions were patients treated in nursing homes for another surgeon ;
in one of these cases a bacteriological problem of great interest and
importance was clarified, the other was a child suffering from staphylo-
coccal septicæmia and too ill to be moved.   Many of the patients
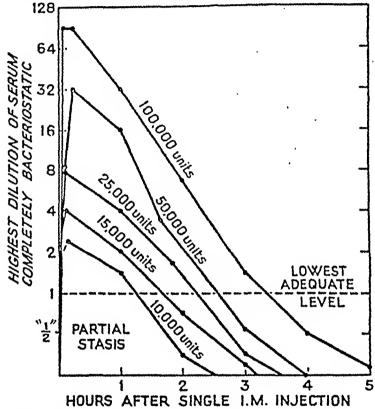
Fig. I—Average results of bacteriostatic estimations of
serum after single intramuscular injection.

· (By kind permission of *The Lancet.*)

have made contributions to hospital funds and to our penicillin research
funds, and it is a matter of some interest that the largest contributions
have come from the least affluent patients. During this period regular
meetings were instituted at which all those interested in the work
pooled their experiences. We have found these meetings very valuable,
and they continue. During the third period generous supplies have
been available through the War Office and the Department of Health
for Scotland, first and rightly for the treatment of war wounds, and
later for general civilian use ; and the present position is that no
patient who could be rightly treated by penicillin lacks the drug. When
any powerful new remedy is introduced to therapeutics, there is often

a tendency to neglect older methods known to be efficient. On the whole this tendency has been well resisted, although certain patients for whom penicillin has been asked could have been treated with equal success by one of the sulphonamides. We are now entering upon a period when penicillin will take its proper and highly important place in therapeutics.

PHARMACEUTICAL CONSIDERATIONS

PROPERTIES.—Penicillin comes to us in ampoules or tablets as the sodium or calcium salt. The chief pharmaceutical problem in dis-
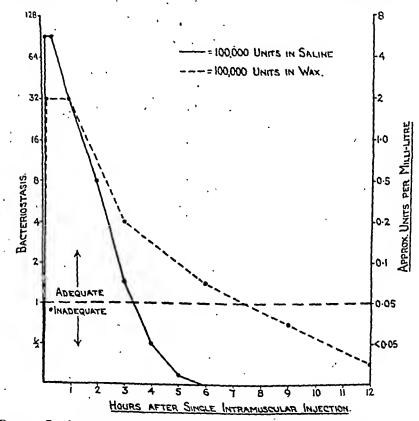
FIG. 2.—Graph comparing excretion of penicillin after intramuscular injection in saline solution and in a mixture of beeswax and peanut oil.

pensing it is that it is highly hygroscopic, the calcium salt less than the sodium salt; an important point in storage is to keep the powder dry, and broadly speaking the cooler it is kept the longer do preparations of penicillin, and especially solutions, retain their potency. The ideal is to store at 4° C. Penicillin is relatively unstable. It is destroyed by *penicillinase*, which is produced by various bacteria including *B. coli*; by acids; by alkalis; by the salts of heavy metals such as mercury; by alcohols; and by oxidising agents such as

hydrogen peroxide, potassium permanganate and Eusol. It is obvious that apparatus for the administration or application of penicillin must be free from any of these substances, nor must they be applied to wounds before or during treatment.

PREPARATIONS.—(a) *Solutions*. Penicillin may be administered in the form of a solution either for parenteral administration or as a local application. For parenteral administration, 100,000-500,000 units may be dissolved in 100 c.c. of sterile saline and given as a
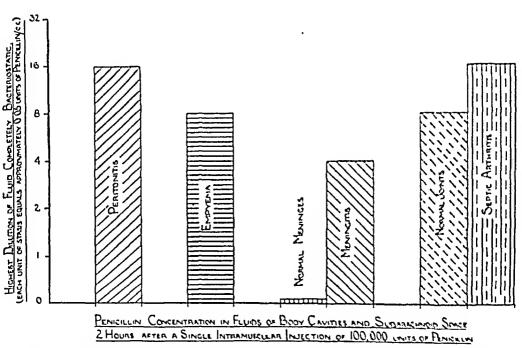
FIG. 3.—Diagram showing the concentration of penicillin in infections of the serous cavities and subarachnoid space after a single intramuscular injection of 100,000 units of penicillin. The figures for the uninfected subarachnoid space and joint cavities are also shown.

continuous intramuscular drip. An accurate apparatus for doing this has been evolved in Edinburgh and described by McAdam, Duguid and Challinor (1944), and it has proved simple and efficacious. Penicillin may also be given by intermittent intramuscular injection, doses of 25,000 units dissolved in 2 or 3 c.c. of saline being administered every three hours. When given intramuscularly it is rapidly excreted in the urine (Fig. 1), and much work has been done in attempting to incorporate it in a vehicle which will delay its excretion. One of these vehicles is a mixture of beeswax and peanut oil, but while this does delay excretion to a certain extent (Fig. 2), it is rather difficult to use. Penicillin administered intramuscularly and distributed by the blood stream does not readily pass into normal serous cavities, with the possible exception of joints and the peritoneal cavity. However,

when such cavities are inflamed, adequate concentrations of penicillin appear in the infected exudate after parenteral administration (Fig. 3). When large doses of penicillin are introduced into infected serous sacs, quantities adequate to produce bacteriostasis appear in the blood stream, and indeed remain in sufficient concentration for longer periods than do similar doses given intramuscularly (Fig. 4). These points have an obvious bearing on the choice of route in the treatment of such conditions as peritonitis, empyema and meningitis. For the
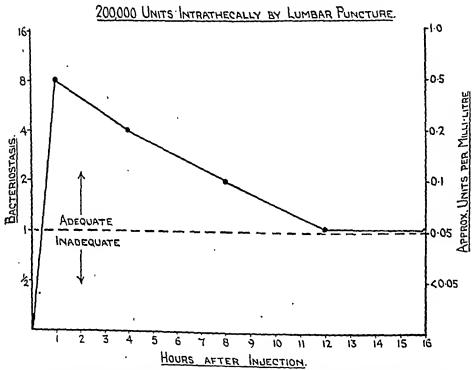
FIG. 4.—Graph showing concentration of penicillin maintained in the blood stream after the introduction into the subarachnoid space of 200,000 units. (By kind permission of *The Lancet.*)

spraying of cutaneous conditions, and for eye drops, penicillin is also put up in solutions in strengths varying from 500 to 2500 units in each cubic centimetre.

(*b*) *Powder.* Penicillin may be applied to wounds or raw areas as a powder, diluted as a rule with sulphathiazole, so that 1 gram of powder contains 2000 units of penicillin. The most economical method is to use a special insufflator so as to produce an even frosting of the area to be covered.

(*c*) *Cream.* Penicillin may be made up in a water-soluble base (lanette wax SX), the usual strength being 500 units to the gram.

(*d*) *Lozenge.* Penicillin may be incorporated in agar or gelatin for use in affections of the mouth and throat, each lozenge containing 1000 units.

(e) *Snuff.* With dried plasma as a diluent, penicillin has been used in the form of snuff in the treatment of nasal infections, in a strength of 5000 to 10,000 units per gram.

(f) *Capsule.* A day or two ago Sir Alexander Fleming was good enough to send to me a series of gelatin capsules containing penicillin, to be administered by mouth.

REACTIONS.—In all probability the reactions sometimes observed after penicillin therapy are due to the presence of impurities. Occasionally œdema of the face follows the administration of systemic penicillin (Fig. 5); an urticarial rash may appear (Fig. 6), although this may depend upon the septicæmic infection; and it is said that penicillin by itself may give rise to pyrexia, although it seems more likely that this may be due to the presence of pyrogenic substances in the particular sample. Local reactions at the site of injection seem to depend on the presence of impurities or to be the result of poor technique.

CLINICAL USE

The predominant consideration in clinical use is that penicillin does one thing and one thing only: that is, it deals with bacteria which are sensitive to it and which it can reach. It cannot therefore affect dead tissue, nor does it influence the structural effects of infection, for example the thickening of the skin and subcutaneous tissues seen in chronic sycosis. Since successful penicillin therapy is possible only when the organism is sensitive, it follows that early bacteriological diagnosis is vital. The following table indicates the sensitivity to penicillin of various organisms and other infecting agents.

TABLE I

Penicillin Sensitivity

Sensitive	Insensitive
Staphylococci	Enterococcus
Streptococcus pyogenes and other hæmolytic streptococci (except Group D)	Friedländer's bacillus
	Hæmophilic bacilli
Streptococcus viridans (most strains) and other non-hæmolytic streptococci (most strains) except enterococcus	*Bacillus pertussis*
	Bacilli of the typhoid, paratyphoid, dysentery and coliform groups
Pneumococcus	*Vibrio choleræ*
Bacillus diphtheriæ	*Bacillus pyocyaneus*
Diphtheroid bacilli (most strains)	*Bacillus proteus*
Morax-Axenfeld bacillus	*Bacillus pestis*
Bacillus anthracis	Brucella group
Actinomyces	*Bacillus tuberculosis*
Bacillus welchii and other sporing anaerobes	Yeasts
	Moulds
Gonococcus	Viruses
Meningococcus	Plasmodium and other protozoa
Diplococcus catarrhalis	
Treponema pallidum	

When an accurate bacteriological diagnosis has been made, the indications for the use of penicillin can be translated into terms of clinical diagnosis. The following four tables, taken with some alteration from the pamphlet issued by the Ministry of Health, summarise this translation.

TABLE II

Penicillin is indicated in :—

- (*a*) Septicæmia (systemic administration).
- (*b*) Puerperal sepsis (systemic administration).
- (*c*) Acute cellulitis (systemic administration).
- (*d*) Acute osteomyelitis (systemic administration).
- (*e*) Cavernous and lateral sinus thrombosis (systemic administration).
- (*f*) Pneumonia (systemic administration).
- (*g*) Meningitis (intrathecal injection, often combined with systemic administration).
- (*h*) Carbuncles and acute abscess (systemic or local administration).
- (*i*) Certain types of empyemata (systemic and intrapleural injection).
- (*j*) Suppurative arthritis (intra-articular injection, sometimes combined with systemic administration).
- (*k*) Anthrax (systemic administration).
- (*l*) Actinomycosis (certain strains) (systemic administration).
- (*m*) Gonorrhœa, acute and chronic (systemic administration).
- (*n*) Gas gangrene and " malignant œdema " (systemic administration).
- (*o*) Other acute infections due to organisms sensitive to penicillin but resistant to sulphonamides.

TABLE III

Penicillin is often of value in :—

- (*a*) Burns (cream or spray).
- (*b*) Sycosis barbæ (cream or spray).
- (*c*) Impetigo (cream or spray).
- (*d*) Dermatitis with infection (cream or spray).
- (*e*) Conjunctivitis and infections of cornea (eye drops, cream or lamellæ).
- (*f*) Infected wounds (powder, cream, or in solution).
- (*g*) Encouraging results have recently been obtained in infections of the mouth and throat, using pastilles containing penicillin.
- (*h*) Penicillin may be used as a prophylactic agent in wounds exposed to infection.
- (*i*) Infections of the urinary tract due to sensitive organisms (systemic administration).

TABLE IV

Penicillin may be of value in :—

- (*a*) Syphilis.
- (*b*) Subacute bacterial endocarditis.
- (*c*) Diphtheria.
- (*d*) Acute mastoiditis and otitis media.
- (*e*) Peritonitis.
- (*f*) Chronic osteomyelitis.

TABLE V

Penicillin is of doubtful value or of no value in :—

- (*a*) Tuberculosis.
- (*b*) Acute rheumatic fever.
- (*c*) Rheumatoid arthritis.
- (*d*) Ulcerative colitis.
- (*e*) Infections caused by viruses such as influenza, anterior poliomyelitis and encephalitis lethargica.
- (*f*) All Gram-negative bacillary infections such as typhoid fever, dysentery, undulant fever, and infections with *Bact. coli, H. influenzae, Proteus, Ps. pyocyanea* and *Bact. friedländeri.*
- (*g*) Glandular fever.
- (*h*) Pemphigus.
- (*i*) Hodgkin's disease and the reticuloses.
- (*j*) Leukæmia.
- (*k*) Malaria.
- (*l*) Cancer.

I shall now deal with certain of these conditions in greater detail.

SEPTICÆMIA.—Systemic penicillin therapy to the amount of 100,000 units a day has greatly improved the prognosis in septicæmia, especially in staphylococcal septicæmia, and recovery can be anticipated when the strain is penicillin-sensitive, provided that adequate treatment is begun early and that any collection of pus which forms can be drained. For one to five days after the beginning of treatment, and depending on the severity of the infection, the patient may continue to be very ill, although in streptococcal cases the blood culture becomes sterile in one to three days, and in staphylococcal cases in three to five days. With the control of septicæmia, there is rapid improvement in the general condition, the temperature falls by lysis, and in moderate cases the leucocyte count falls with the temperature (Fig. 7). In grave cases an originally low leucocyte count may rise when the septicæmia has been controlled. Systemic treatment should be continued until any local lesions are also sterilised, a process which may be aided by local use of the drug. It must be emphasised that the usual general measures in the treatment of septicæmia must be energetically applied.

ACUTE OSTEOMYELITIS.—In acute osteomyelitis early and adequate systemic penicillin therapy reduces the immediate mortality and limits the amount of bone destruction. Dr McAdam (1945) has recorded a series of 40 cases, in half of which the blood culture was positive, with one death. Active surgical interference is reduced to a minimum. In the early stages aspiration or drainage of local abscesses may be required, and in the later stages the removal of small sequestra. Systemic treatment must be continued for fourteen to twenty-one days, and terminated only when any local lesion is sterile. In acute osteomyelitis, penicillin may be administered by the intramedullary route suggested by Mr Aird (1945). This usually produces adequate

concentration in the serum and has two further advantages : first it ensures a high concentration of the blood in the infected medulla, and second it is possible to aspirate samples of the infected marrow at intervals, for bacteriological examination. Unless one is familiar with it, the radiological picture in these cases is apt to be misleading. There is widespread rarefaction of bone which makes it difficult to recognise any architecture. This is due not to local destruction but to the presence of active vascular tissue as a result of whose activity the bone is recalcified and its architecture restored almost to normal (Fig. 8). It should be noted that in osteomyelitis early diagnosis is
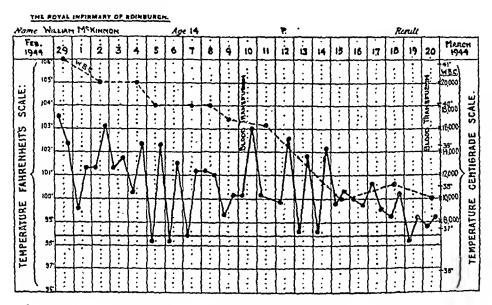
FIG. 7.—Temperature chart in Case 1, showing fall of temperature by lysis and parallel fall in leucocyte count.

essential for success ; should the disease become chronic, it is but little affected by either systemic or local treatment by penicillin.

SEPTIC ARTHRITIS.—The ideal local treatment of either primary or secondary suppurative arthritis is daily aspiration of the joint and the injection of 25,000 units of penicillin in 2 to 5 c.c. of saline, a procedure which is continued until the pus becomes sterile and effusion disappears. However, local treatment is not absolutely essential, because penicillin administered systemically reaches the infected effusion in adequate concentration.

CASE 1. W. McK. This young man was transferred to my ward from Professor Murray Lyon's ward, suffering from staphylococcal septicæmia with lesions in the left tibia, right olecranon and left acromio-clavicular joint. In addition he had a staphylococcal pneumonia and staphylococcal pericarditis. He improved slowly under penicillin therapy ; a subperiosteal abscess over the left tibia required drainage but it proved possible to suture

the wound secondarily, although later two small sequestra had to be removed. The pericarditis yielded to penicillin therapy (see p. 26 and Fig. 11). The youth has made a good recovery and appropriately enough is now employed by the Royal Infirmary to deliver penicillin where it is needed throughout that institution.

CASE 2. J. G. This child, a patient of Mr Aird, suffered from osteomyelitis of the upper end of the femur, complicated by septic arthritis of the hip joint from which *Staph. aureus* was recovered. He was treated by intramedullary drip, and in the course of four months the upper end of his femur has been entirely reconstituted and he has full movement in the hip joint (Fig. 8, *a*, *b*, *c*, *d*).

ACUTE LOCAL PYOGENIC INFECTIONS.—Local staphylococcal infections and local streptococcal infections, which may improve under sulphonamide therapy, are well controlled by systemic administration of penicillin. The local process may resolve or an abscess may form, possibly containing necrotic tissue. Abscesses are drained as necessary, and necrotic tissue should always be removed (with the possible exception of tiny sequestra in bone). When the pus in an abscess cavity is thin it should be evacuated by aspiration and replaced by a somewhat smaller volume of saline solution containing 25,000 units of penicillin, the procedure being repeated every second day until the abscess is healed. Wounds already infected, or those in which infection appears probable, may be treated by introducing penicillin solution into their depths through fine tubes, up to a total of 10 c.c. twice a day for four days ; or the wound may be liberally covered with penicillin-sulphathiazole powder.

CASE 3. J. C. This patient was admitted to my ward suffering from a large abscess occupying the left iliac fossa and left groin. The infecting organism proved to be a hæmolytic streptococcus. Some days after drainage had been established he became severely ill and the blood culture yielded a hæmolytic streptococcus. The following day, after the administration of 50,000 units of penicillin, the blood culture was negative, but seven days later septic arthritis due to a hæmolytic streptococcus of the same type appeared in the left ankle. This was dealt with by the administration of systemic penicillin, and after twenty-four hours, during which 100,000 units were administered, the effusion in the ankle joint was sterile.

INFECTIONS OF THE FINGERS AND TENDON SHEATHS.—In the Royal Infirmary Mr Curr has carried out an extensive investigation on the use of penicillin in infections of the hands, and in Leith Hospital Mr Murray has done the same ; I am indebted to the former for a summary of his views. In general, local methods of application give no better results than in controls, but in tenosynovitis, severe lymphangitis and early septic arthritis the results of systemic administration are very good. It must be emphasised, however, that whatever the type of infection, correct surgical treatment is essential and the patient must be continuously and adequately supervised.

FIG. 5.—Œdema of the face during the administration of penicillin.

FIG. 6.—Urticarial reaction during the administration of penicillin.

(a)

(b)

(c)

(d)
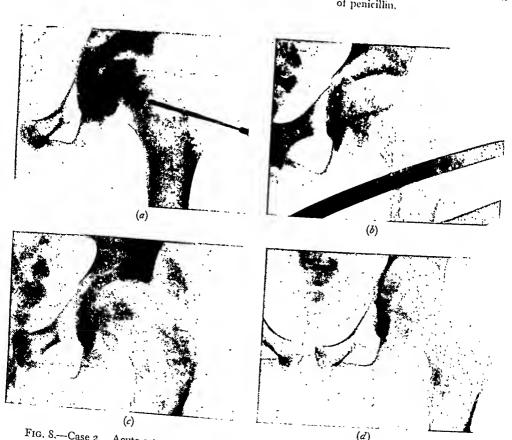
FIG. 8.—Case 2. Acute osteomyelitis of upper end of femur with acute arthritis of hip joint.
(By kind permission of *The British Journal of Surgery*.)

(a) 10.11.44. Early lesion showing intramedullary needle *in situ*.
(b) 22.11.44. Later stage of lesion showing widespread rarefaction in femur and articular changes.
(c) 4.1.45. The rarefactive process in the femur is at its height. The joint outline has been restored.
(d) 1.3.45. Showing restoration of the architecture of the neck of the femur and a normal joint outline.
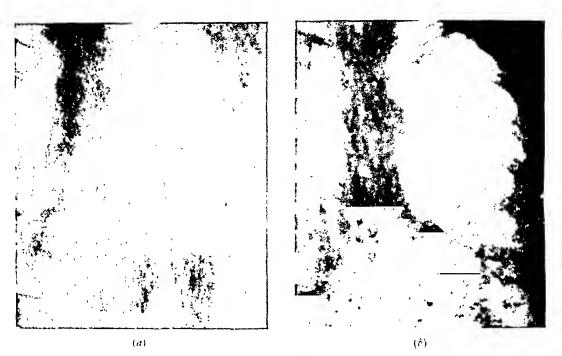
FIG. 10.—Case 5. Left-sided pneumococcal empyema.

(a) 28.10.44. Before treatment.
(b) 15.11.44. After cure by local penicillin treatment.
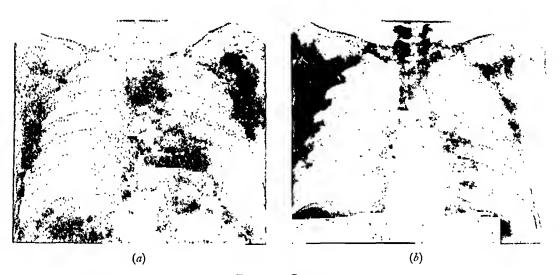
FIG. 11.—Case 1.

(a) 7.3.44. Suppurative pericarditis before local penicillin treatment.
(b) 17.3.44. Appearances after sterilisation of the intrapericardial fluid.

When surgical treatment is delayed and necrosis has been allowed to occur, penicillin cannot be expected to compensate for bad surgery. In 25 cases of tenosynovitis affecting the digits of the hand, the function of the digit was completely recovered in 12, slightly limited in 7, while in 6 the digit remained permanently stiff. Under systemic treatment streptococci disappeared from the infected sheath in two to three days, and staphylococci in 7 days or longer.

CASE 4. E. M. This patient had an infection of the tendon sheath of the left thumb due to a hæmolytic streptococcus. On admission she was very toxic and had repeated rigors. The tendon sheath of the thumb was drained in the digit and in the palm, and intramuscular penicillin begun. The following day it was necessary to drain the sheath of the little finger in the digit and in the palm, and Parona's space in the forearm. Thereafter improvement was steady; penicillin was continued for five days although the tendon sheath became sterile in two days. The wounds were completely healed in sixteen days, and there has been full functional recovery in all parts of the hand and wrist.

PROPHYLAXIS.—Penicillin may be used either locally or by systemic administration for wounds which result in large raw surfaces, and before the grafting of skin or the grafting of bone, for example in the mandible. Used in this way, it is a valuable adjunct to surgical treatment, but it should be emphasised that in no way does it dispense with the need for scrupulous primary treatment and care in subsequent dressings.

EMPYEMA.—Although large doses of systemic penicillin reach the cavity of an empyema in sufficient concentration to sterilise it (Fig. 9), local injection into the cavity is more economical and produces a higher local concentration of the drug. Pus is aspirated on alternate days, and 25,000 units of penicillin in 5 c.c. of normal saline introduced, a procedure which is repeated until three successive specimens of pus at intervals of twenty-four hours have proved to be sterile. In pneumococcal and streptococcal cases this can be expected in seven days, in staphylococcal cases in about twenty-one days. Although it is possible in rare cases to cure an empyema by aspiration in this way, our present procedure is to sterilise the pus, to start systemic penicillin, and then to carry out open drainage in order to avoid the thickening of the pleura which impedes the re-expansion of the lung, to secure the removal of any masses of fibrin which may be present and to provide drainage for pus which may be too thick to aspirate. Operation is also necessary when an empyema is loculated. When empyema occurs in the presence of pneumonitis, systemic treatment as well as local is obviously also necessary.

CASE 5. J. F. This youth suffered from a pneumococcal empyema which was treated locally by penicillin. He is the only patient in whom operation has not been necessary (Fig. 10, *a*, *b*).

CASE 6. R. T. This patient represents the usual sequence of events. He had a pneumococcal empyema which became sterile in two days after the systemic administration of 600,000 units of penicillin. A week later pneumococci were again obtained from the pus. This was again sterilised by systemic penicillin, and thereafter open drainage by rib resection was carried out. Large masses of fibrin were found and removed, and the patient subsequently made an uninterrupted recovery.
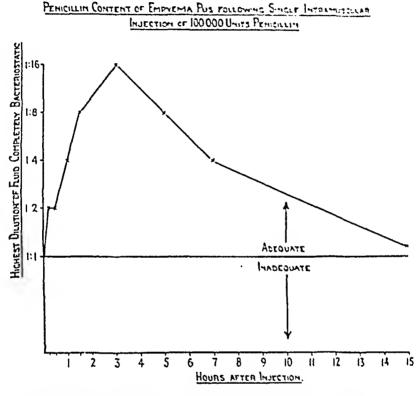
FIG. 9.—Graph showing penicillin content of empyema pus after a single intramuscular injection of 100,000 units. (By kind permission of *The Lancet*.)

SUPPURATIVE PERICARDITIS.—In suppurative pericarditis repeated aspiration of the pericardium and injection of 25,000 units of penicillin are indicated. The procedure is carried out on alternate days until the pus is sterile (Fig. 11, *a, b*).

MENINGITIS.—The drug has been used in pneumococcal, streptococcal, and sulphonamide-resistant meningococcal meningitis, and, with the most valuable co-operation of Mr Dott, it has been possible to make certain observations, chiefly in pneumococcal cases, of the routes to be employed. In infections of the subarachnoid space, it is possible to obtain bacteriostatic concentrations in the cerebrospinal fluid by giving large doses, *e.g.* 50,000 units four-hourly, by the intramuscular route. The concentration in the fluid can be increased by intrathecal injections of 25,000 units of penicillin in 2 c.c. saline given daily. Both routes should be employed, especially in cases in which there is

reason to suspect interference with the circulation of the cerebrospinal fluid as the result of adhesions, because penicillin can reach trapped collections of fluid only after systemic administration.

BACTERIAL ENDOCARDITIS.—During the past year the problem of treating bacterial endocarditis by penicillin has been intensively studied in a research planned by the Medical Research Council to include the whole country. In Edinburgh, Dr Rae Gilchrist has undertaken this task, and I have his authority to say that he considers penicillin by far the best remedy so far employed. Naturally early diagnosis is of supreme importance so that treatment may antedate failure of nutrition and, so far as possible, the occurrence of major embolic phenomena, which if survived may apparently undermine resistance and prolong the illness. The assessment of remedies in this disease is notoriously difficult on account of its fluctuating course and spontaneous remissions.

ACTINOMYCOSIS.—Strains of the streptothrix causing the clinical condition actinomycosis vary greatly in their susceptibility to penicillin, and even when the strain is susceptible large doses may be required. Abscesses are drained as they appear.

Other conditions in which systemic penicillin treatment has been successful include thrombosis of the intracranial sinuses, sulphonamide-resistant pneumococcal pneumonia, staphylococcal pneumonia, puerperal sepsis and staphylococcal urinary infections.

OTORHINOLARYNGOLOGY.—Dr Mitchell, Dr Simson Hall's clinical assistant, has kindly provided me with some information on the applications of penicillin in otorhinolaryngology. It has been found that in an otherwise healthy mouth all susceptible organisms (and that means practically all organisms) are eliminated in twelve to eighteen hours by the administration of three to four lozenges at two-hourly intervals, the lozenge being allowed to dissolve slowly. Lozenges have been given both pre-operatively and post-operatively in tonsillectomy cases, the local condition of the fauces being better both immediately after operation and during the process of healing, which is considerably accelerated and less painful. In acute streptococcal tonsillitis, lozenge treatment is not so successful since re-infection occurs from tonsillar crypts, although infective droplet spray is controlled ; but lozenges may eliminate sulphonamide-resistant streptococci from the throats of carriers for as long as administration is continued. In acute sinus infections there is no longer reason to dread either osseous or intracranial complications, but chronic sinus infections share the lack of response evident in chronic infections elsewhere throughout the body. Penicillin lozenges have been extremely valuable in the treatment of Vincent's infection. Dr Hutchinson, the Dean of the Edinburgh Dental Hospital, informs me that approximately 50 cases have been treated. Six lozenges are distributed throughout waking hours and one lozenge placed in the buccal sulcus on going to bed. There is marked clinical improvement in twenty-four hours, and after

four or five days' treatment the lesions have disappeared. Some of these cases relapse, for what reason it is at present impossible to say. Dr Cranston Low has investigated the bacteriological findings in these cases, and has elicited the extremely interesting fact that Vincent's spirochæte disappears within forty-eight hours, although other spirochætes are more resistant. The fusiform bacilli may diminish in number, but as a rule persist throughout treatment.

DERMATOLOGY.—In sycosis, Dr Percival has found penicillin a valuable aid both as primary treatment and in cases which have relapsed. A solution is sprayed on the affected area several times daily in the early stage sof treatment ; later penicillin is applied as a cream three or four times daily. In long-standing cases other therapeutic measures may be required to deal with the pathological changes in the skin which result from the chronicity of the infection. In impetigo and the infective eczemas, Dr Percival has found penicillin disappointing, with the exception of recurrent pustular eczema of the fingers and palm which responds well.

OPHTHALMIC CONDITIONS.—Through Dr Cameron's kindness, I am able to show you a remarkable case.

CASE 7. This patient had a cataract removed in 1940. In 1944 he returned with septic iritis and an abscess in the vitreous caused by an infection through a weak point in the operation scar. Through a keratome incision a lacrimal needle was introduced through the pupil into the vitreous and 2500 units of penicillin in 0·5 c.c. saline injected, a procedure which was repeated two days later. The infection in the vitreous was controlled, the remains of the abscess persisting temporarily as a fibrous mass which ultimately disappeared, leaving the patient with 6/18 vision and ability to read Jaeger I with suitable correction.

Dr Graham has been comparing the effects of penicillin treatment with albucid in traumatic corneal ulceration. He has found that after penicillin the corneal scar is probably less dense, but considers that there is little to choose between the two methods. Of 13 cases treated by penicillin drops, 11 have 6/18 vision or better. In 2 late cases with extensive corneal disturbance the ulceration healed, but the resulting scarring left the patient with poor vision.

VENEREAL DISEASES.—Dr Batchelor has treated 115 cases of gonococcal infection in men and 26 cases in women and children. He found that a method of treatment giving a high cure-rate consists of four intramuscular injections each of 40,000 to 50,000 units given at intervals of three hours. This method of treatment could be adopted in general practice provided that the necessary facilities for storing and administering penicillin were available. There is, however, one important reason why cases of gonorrhœa should come under the care of a competent venereologist, a reason so important in its implications that I quote Dr Batchelor's views on the matter :—" Every case of gonorrhœa treated with penicillin should receive a rigorous test of cure,

such testing to include periodical bacteriological examinations of secretions from all the areas liable to be infected, and also testing of the blood, not only by the gonococcal complement fixation, but also by the Wassermann and Kahn tests. This latter precaution is rendered very necessary by the fact that the dosage (160,000 to 200,000 units in four doses of 40,000 to 50,000) recommended as adequate for the cure of gonorrhœa would be quite insufficient to cure syphilis (possibly contracted at the same time and incubating more slowly), and would only suppress or delay the appearance of the chancre, thereby preventing or delaying the recognition of the concomitant syphilis. It is therefore an essential routine that all cases of gonorrhœa treated with penicillin should have Wassermann and Kahn tests of the blood repeated at least once a month, and that clinical and serological observation for syphilis should be continued for six months."

The treatment of syphilis by penicillin is still a matter for exploration by the experts.

CHOICE BETWEEN SULPHONAMIDES AND PENICILLIN

When an organism is sensitive to both penicillin and a sulphonamide, penicillin is generally more effective, but many infections by hæmolytic streptococci and pneumococci yield readily to a sulphonamide. When sulphonamide-resistant strains of these organisms are encountered, penicillin will achieve a cure. On the other hand, in all severe staphylococcal infections, treatment by penicillin should be the primary choice. In the case of other organisms the choice may be determined by the known sensitivity of each bacterium to the two drugs.

THE FUTURE

Although at the present time adequate supplies of penicillin are available by the concentration of medium in which the mould has been grown, work on synthesis of the drug proceeds, and when this is achieved we may look forward to an even more powerful influence upon organisms, and as a result of the work of organic chemists, to the introduction of substitution products which will affect hitherto insensitive bacteria. At the moment, and properly used, penicillin is an almost spectacularly valuable addition to therapeutics. The proper use of penicillin involves three cautions : first, that suitable cases should be chosen for penicillin treatment, if at all possible by bacteriological methods ; second, that the temptation to rely too exclusively on penicillin in the treatment of any given condition should be vigorously resisted ; and third, that in the treatment of any given condition all other general (for example supportive) and local (for example surgical) methods of previously proven value should be energetically utilised.

CONCLUSION

Throughout this lecture it must have been obvious that no one person could be competent to appraise the value of penicillin therapy in each of the many different conditions in which it has been found useful; but when research has been co-ordinated I feel that it is valuable occasionally to make available in broad perspective the results that have been obtained. It must also have been evident that I am under great obligation to those clinicians and bacteriologists who have co-operated throughout the programme of research. In this programme the clinical catalyst, if I may use an inorganic term for so vital a colleague, has been Dr McAdam, and to him especially I tender my thanks. My thanks are tendered also to my bacteriological colleagues, headed by Professor Mackie, thanks not only for the observations made on individual cases, but for a broader conception of the place of bacteriology in clinical work.

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PENICILLIN IN THE TREATMENT OF VENEREAL DISEASE: A YEAR'S EXPERIENCE IN A CIVILIAN CLINIC

By R. C. L. BATCHELOR, F.R.C.S.Ed., W. H. DONALD, M.B., M. SCOTT GRAY, M.B., R. P. JACK, M.B., D.P.H., and M. MURRELL, F.R.C.S.Ed.

GONORRHŒA

IN the past twelve months 116 cases of gonococcal infection in men and 26 cases in women and children have been treated with penicillin. Various dosages have been used and every case has been cured, if not by the first course, a further more intensive course has been sufficient.

The greatest cure rate has been given by multiple intramuscular injections of saline solution of penicillin in varying dose at three to four-hourly intervals. Single injections of a dose of 100,000 Oxford units (O.u.) in saline solution and single or multiple injections of 50,000 to 100,000 Oxford units in suspension in beeswax and nut oil have not given such a high rate of cure. The presentation of the penicillin in beeswax-nut oil suspension was designed to delay the rate of absorption (and therefore also the rate of excretion), thus maintaining for a longer time an adequate concentration of penicillin in the blood stream, prolonging its action on the gonococci, and, by so doing, enhancing the prospect of cure.

The ideal method of treatment for out-patients is a single intramuscular injection giving a high rate of cure. So far this ideal has not been attained, but at the moment a single injection of a large dose (200,000 units) in saline solution is being tried to see if this will give a sufficiently high rate of cure to justify its use.

Gonorrhœa in Men.—Varying dosages of penicillin, ranging from 15,000 to 200,000 Oxford units, have been given either by single or by multiple intramuscular injection. Multiple (2 to 10) injections either of saline solution or of beeswax suspension, exhibited in 70 cases, yielded a cure rate of 87 per cent.; whereas single injection treatment, used in 33 cases, gave a cure rate of 60 to 61 per cent. But, in 13 cases, where a single injection of a high dose (200,000 Oxford units) was the method used, the cure rate was 84·6 per cent.

It was found that a course of four injections of 40,000 O.u. at three-hourly intervals gave a cure rate of 100 per cent. in 10 cases, and this dosage was for a time adopted as the standard treatment for a case of gonococcal urethritis.* This regime was well adapted for use in out-patients, being easily completed in one day, say between 9 a.m. and 6 p.m.

* Subsequently relapses occurred with this technique and it became evident that a larger number of three-hourly injections, say eight instead of four, of 40,000 units, would be necessary to achieve something approaching complete success in a large group of cases.

Of the 116 cases of gonococcal infection in men, 44 cases had resisted sulphonamide therapy, and 24 cases relapsed on the initial dosage of penicillin, but all were cured by a further more intensive course of penicillin. It could not be shown that cases which were resistant to sulphonamide therapy were either more or less liable to relapse with penicillin therapy than those cases which had had no previous treatment.

The subjoined table shows the results given by the different dosages of penicillin used in the treatment of gonorrhœa in men.

TABLE I

Gonorrhœa in Men

Dose.	Interval in Hours.	Number of Cases.	Number of Cases Sulphonamide Resistant.	Number of Relapses.	Percentage Cure.
Saline Solution.					
1 × 100,000	...	13	5	5	61·5
2 × 100,000	12	1	1	. .	...
10 × 10,000	3	1	...	...	...
2 × 60,000	24	1	1	1	...
4 × 15,000	4	11	5	5	54·5
8 × 20,000	3	5	1	...	100·0
4 × 40,000	3 or 4	10	4	...	100·0
5 × 30,000	2	9	4	...	100·0
5 × 20,000	2	2	1	...	...
50, 15, 15, 50,000	4	5	4	...	100·0
1 × 200,000	...	13	3	...	84·6
2 × 200,000	24	2	1	...	...
Beeswax and Nut Oil.					
1 × 100,000	...	20	6	8	60·0
2 × 100,000	9-12	14	3	2	85·7
4 × 50,000	12	9	5	1	89·0

Comment.—In those cases which relapsed, the relapse occurred more quickly (average three to four days) after one or two doses, and less quickly (average five days) after multiple (four to eight) injections. Urethral smears became free of gonococci on an average of three to four hours after the commencement of penicillin therapy. Local intolerance, such as pain and stiffness at the site of injection, has been slight, and has to a large extent passed off in from one and a half to two hours after injection. General intolerance to penicillin has been minimal ; occasionally slight headaches or disturbed sleep with dreams have been recorded. In over 75 per cent. of all the 116 cases, the urethral discharge ceased after the first day, but, according to the duration and severity of the inflammatory reaction, an increased secretion of mucus might persist for several days. Apart from a relatively high relapse rate from the use of suspensions of penicillin in beeswax and nut oil, the difficulties of administration of this preparation were so great as to render it an unsuitable method for the large-scale treatment of out-patients, and further development

of this technique has been postponed.   An attempt is now being made to prolong a bacteriostatic concentration of penicillin in the blood by the employment of adrenaline, according to the method suggested by Fisk, Foord and Alles (February 1945).

Gonorrhœa in Women and Children.—Of the 26 cases of gonococcal infection in women and children, only one case relapsed on the initial dosage (four injections each of 40,000 units), and this patient was cured by a further course of penicillin.   The results of the different dosages used are displayed in the subjoined table :—

<div align="center">TABLE II</div>

<div align="center">*Gonorrhœa in Women*</div>

Dose.	Interval (Hours).	Number of Cases.	Number of Cases Sulphonamide Resistant.	Number of Relapses.	Percentage Cure.
Saline Solution.					
4×40,000	3	12	7	1	91·6
100,000 50,000 50,000	3	1	1	...	...
100,000 50,000 50,000 50,000	4	1	1	...	...
4×15,000	3	1	1	...	...
3×20,000	3	1	1	...	...
100,000 50,000 25,000 15,000	6 hours on successive days	1	...	...	...
50,000 (I.M. drip)	...	1	...	...	...
350,000 (I.M. drip—7 days)	...	1	...	...	...

<div align="center">The one case which relapsed received 2×200,000 (American) at an interval of 4 hours, and this resulted in cure.</div>

Beeswax and Nut Oil.					
4×50,000	8 hours on successive days	2	2	...	...
100,000 50,000 50,000	4	1	1	...	...
100,000 50,000 25,000	5 and 19	1	...	...	...

Comment.—Of the 23 cases in adults, 3 were complicated by pregnancy and one by the puerperium.   Other complications included salpingitis (2 cases), secondary syphilis (one case), and neurosyphilis (one case).   Concomitant trichomonas vaginalis infestation was present in 5 cases : this protozoal infestation showed a temporary improvement after penicillin, but relapsed quickly.   Fourteen of the 23 cases had resisted the action of sulphonamide drugs, usually sulphathiazole. Smears taken daily and not at short intervals became negative on an average less than a day and a half after penicillin.   Smears taken at frequent intervals contained no gonococci on an average less than five and a half hours after penicillin.

Three children were treated, one being a case of gonococcal ophthalmia, and two had gonococcal vulvo-vaginitis.   The individual dose of penicillin used varied, according to the child's age, from

10,000 units for the baby with ophthalmia to 30,000 or 50,000 units for the girls with vulvo-vaginitis, the number of injections given being four for the baby and for the girl who received the 30,000 unit dose, and three injections for the girl receiving the 50,000 unit dose. In the case of ophthalmia, and in both the cases of vulvo-vaginitis, the smears were negative on the day after commencement of treatment. Both the cases of vulvo-vaginitis had proved sulphonamide-resistant.

SYPHILIS

Thirteen cases of early syphilis in men (9 sero-positive primary, 3 secondary, and one latent), and 9 cases of early syphilis in women (3 primary sero-negative and 6 secondary) have been treated with penicillin. The scheme of treatment has been the same for both sexes, and has consisted of sixty intramuscular injections each of 40,000 units in saline solution given at intervals of three hours to a total of 2,400,000 units in seven and a half days. In addition, 8 cases of syphilis in men (3 primary sero-negative, one primary sero-positive, two secondary and two latent) were treated with half the above total amount of penicillin, namely 1,200,000 units, in sixty divided intramuscular doses each of 20,000 units, along with eight daily intravenous injections each of 60 mgms. of mapharside. Three cases of congenital syphilis, including one of juvenile paresis, were also treated.

Effects.—Spirochæta pallida disappeared from serum obtained from the chancre or from moist papules or mucous patches in six to nine hours. Unless it was very large, the chancre healed superficially within the eight-day period of administration. The spots of the secondary rash faded and disappeared, or were disappearing, by the end of the seven and a half days' treatment. Provided that the patient was not confined to bed, there was little local intolerance in spite of the number and frequency of the intramuscular injections. General intolerance, usually in the form of headache, was slight apart from a Herxheimer reaction, with transient fever, headache, and intensification of the secondary rash, observed in two of the male cases.

The quantitative Wassermann reaction (Q.W.R.) was taken at the commencement of treatment and thereafter daily during the seven and a half days' course. On completion of the course, the Q.W.R. was taken at weekly intervals.

It was found that in the majority of cases the titre of the Wassermann rose during the course of treatment, and in 5 cases was higher at the end of treatment than at the commencement. In the remaining cases the titre of the Wassermann at the end of treatment was the same as or lower than the titre at the commencement. In those cases who attended regularly for observation the Wassermann became negative within two to nine weeks after completion of treatment. In most cases it was found that the higher the titre at the commencement of treatment the longer the time taken for reduction to negativity.

Comments.—The three-hourly injections are given both night and day, and it is necessary to take the patient into hospital. The treatment is completed in seven and a half days as contrasted with the six to eighteen months' duration of routine arseno-bismuth therapy. When penicillin is administered in combination with the arsenical, mapharside, the total dose given of each is subcurative, but when they are used together the synergistic curative effect is expected to be greater, possibly greater than a full dose of either. Penicillin is well received by patients who, through an allergic condition such as asthma, are intolerant of neoarsphenamine, and penicillin has been well tolerated by patients suffering from post-arsphenamine hepatitis with jaundice.

None of the cases described has been observed for a period sufficiently long to justify conclusions being drawn as to the permanence of the beneficial action of penicillin, either when given alone or in combination with an arsenical. Penicillin used alone is not attended by the risk of causing any of the disabling and sometimes dangerous toxic effects which occasionally follow treatment by either arsenical or bismuthial drugs.

GENERAL COMMENTARY

The advantages resulting from the adoption of penicillin in the therapy of either of the major venereal diseases, gonorrhœa and syphilis, include the rapid abolition of infectivity and reduction of spread of the disease ; the absence of toxic reactions involving danger or disability ; the minimum loss of working time ; and the important fact that the treatment is completely under the control of the doctor who gives the doses, whereas with sulphonamide therapy the patient has to be relied upon to treat himself by taking his oral doses regularly.

SUMMARY

A year's experience of the use of penicillin in the treatment of gonorrhœa and syphilis in a civilian clinic is epitomised. One hundred and forty-two cases of gonorrhœa and 33 cases of syphilis are reviewed. The results of penicillin treatment are described, and displayed in tabular form.

CONCLUSIONS

One day's treatment, comprising four or five intramuscular injections of penicillin at three-hourly intervals to a total dosage of 150,000 to 160,000 Oxford units, will effect a cure of gonorrhœa in a very high proportion of cases, whether in men or in women.

Syphilis requires a much higher dosage than gonorrhœa, and the dose sufficient to cure a gonorrhœa may only hinder the recognition of a concomitant syphilis.

Eight days of treatment, comprising sixty intramuscular injections of penicillin at three-hourly intervals to a total dosage of 2,400,000 O.u., will produce apparent clinical cure in early syphilis with reduction or reversal of positive serological tests, in either sex. Penicillin is therefore an exceedingly potent, as it is also a non-toxic remedy, the value of which cannot yet be assessed, but the use of which should serve to shorten greatly the therapeutic schedules of the future.

The year 1944 marked the commencement of the " penicillin era " in the treatment of the two major venereal diseases.

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FISK, FOORD and ALLES (2nd February 1945), *Science*, 101, No. 2614.

INJURIES OF THE CARTILAGE IN MINERS *

By W. A. D. ADAMSON

INJURIES to the cartilages of the knee joint in miners afford a topic of some interest. The miner works below ground in a cramped position with the knees flexed; the cartilages, therefore, are particularly liable to injury when a sudden rotatory and abductory strain is thrown on the joint with the knee in a flexed or semi-flexed position. The miner is thus particularly liable to suffer cartilage injuries. In order to be able to return to his former employment and to earn his livelihood after he has received treatment, he must have a knee which is stable and which is able to withstand numerous strains of the type which caused the original injury; treatment, therefore, must be able to produce a joint which is as good or very nearly as good as before the injury.

A consideration of 60 cases of cartilage injuries with a follow-up of their subsequent course and a consideration of the period of disability will be given. The ability to return to work below ground is of particular interest in affording a measure of the success of the treatment. All the patients in the series worked below ground as strippers, machinemen, stoneminers, developers, brushers, firemen and shotfirers. These various jobs do not differ sufficiently to make it worth while to separate out in detail the occupation of the various cases. The whole series consists of patients whose work is underground.

Diagnosis.—The history is taken with care and gives a clue to the diagnosis as clearly as the physical examination. The miner, from experience gained from his colleagues, has a good idea when a knee injury is of any severity. He is usually able to describe clearly the date and the time of the accident. A measure of the severity of the accident is afforded by the ability of the patient to complete his shift and to walk home. Usually it is found that he had to cease work at the time of the injury and reached home either by ambulance or possibly by bus. In the vast majority of cases immediately after the accident the patient found that he was unable fully to straighten his knee—that his joint was locked. Frequently the locking was relieved by a friend manipulating the joint, and this usually gave relief of the severe pain and enabled him to begin to move with some comfort. Such an injury would be followed by an effusion into the joint. Thirty-four patients of the total number of 60 gave a history of this type. In 20 patients the diagnosis was a little more difficult. The history was of a mild injury followed by swelling of the joint and subsequently by a feeling of instability in the joint. In some cases there was a history of intermittent locking followed by the development of an effusion, but more frequently there was an occasional

catch in the joint followed by the development of an effusion. As a general rule it may be taken that when there has been an injury of any severity to the joint and the joint fails to recover within a few weeks, the probability is that there has been damage to one of the cartilages, provided there is no other evidence of disease or injury to the joint.

Physical Examination.—Wasting of the quadriceps muscles is a very constant sign of an intra-articular lesion. The estimation of the amount of wasting is best made by the consistence of the muscles. Flabbiness of the muscle is thus a better sign than loss of bulk. Tenderness over the cartilage is the cardinal sign of injury. The usual site of the tenderness is over the joint space halfway between the medial collateral ligament and the medial edge of the patella, but tenderness may be elicited farther back over the medial collateral ligament or behind that point when the posterior part of the cartilage has been damaged. Tenderness over the medial collateral ligament may be thought to be due to an injury to this ligament ; in a ligamentous injury the tenderness usually extends to the attachment of the ligament to the femur, to the tibia or to both. Furthermore in injury to the ligament, pain is elicited when the tibia is abducted on the femur. If pain is elicited on adduction of the tibia on the femur, it is probable the cartilage is the seat of the injury. McMurray's sign—that is when gradual extension of the fully flexed knee is carried out while the tibia is made to rotate medially and laterally on the femur when a click may be felt—is a valuable aid in the diagnosis of injuries to the posterior part of the cartilage.

Injuries to the lateral cartilage are rarer and the history is rather vague. The symptoms are referred to the lateral side of the joint with tenderness corresponding.

X-ray examination of the joint is carried out as a routine to exclude the possibility of the presence of a loose body and also to estimate the degree of osteo-arthritis affecting the joint. In this series of cases osteo-arthritis plays a prominent part, for the patients are older in years, and the miner—perhaps as a result of his work—is liable to suffer from radiological evidence of osteo-arthritis. Where the evidence of cartilage injury is clear, operation has been undertaken in spite of the presence of the bone changes of osteo-arthritis. It was felt in these cases that the cartilage injury was of such severity as to preclude the man from working. Removal of the cartilage might enable him to return to work with a knee which one would not expect to be perfect. As will be shown, the recovery rate is usually somewhat slower in the presence of osteo-arthritis, but not so markedly as one might expect.

Operation.—One day's preparation of the skin is given. In 25 of the cases Annandale's incision was used, and in 35 a vertical incision. Exposure is equally good. The leg is allowed to hang over the end of the operating table with the knee in the flexed position. A tourniquet is always used and has been applied in each case either

by myself or by the anæsthetist. The question as to how much of the cartilage should be removed has frequently been asked. In the 25 earlier cases I removed only the loosened fragment of the cartilage, except when the tear affected the posterior part. In the more recent 35 cases I have removed virtually the whole cartilage. As Smillie has shown, the leaving of the posterior part of the cartilage may give rise to further trouble at a later date, and on the evidence he has produced it is clear that removal of the whole cartilage is to be aimed at. It is difficult to assess the likelihood of further trouble developing, but in none of the 25 cases where a part only of the cartilage was removed has any further trouble developed although these cases were dealt with 5 and 6 years ago.

The average age of the cases operated on is $37\frac{1}{2}$ years. Thirteen of the cases in the 20-30 age group, 3 in the 31-40 group, 12 in the 41-50 group and 5 in the 51-55 group.

In 54 cases the medial cartilage was the site of the injury and in 6 cases the lateral, so that 90 per cent. of the cases were of injuries to the medial cartilage. These figures correspond with Jones' view that 90 per cent. of cartilage injuries were of the medial cartilage. In Hamilton and Finkelstein's series of 110 cases in soldiers a similar proportion was found—actually 93 per cent. of their cases were injuries to the medial cartilage, so that this proportion of 90 per cent. is fairly representative. Of the 6 cases of injury to the lateral cartilage 2 were displacements of a congenital disc type of cartilage. This is the condition where the cartilage fails to develop normally and remains as a disc. No symptoms are usually given until the cartilage has been loosened from its attachment by some injury. The cartilage then slips anteriorly and posteriorly with the movements of the tibia. Usually the cartilage slips anteriorly on full flexion of the knee, and posteriorly on full extension, and as it slips forwards and backwards it does so giving rise to a sickening sound in the joint. By palpation it is usually possible to appreciate that this catch in the joint occurs on the lateral side, and often the cartilage can be seen to slip backwards and forwards, producing a sudden bulging of the skin over the joint space lateral to the patella. In the remaining four cases the lateral cartilages were torn in the bucket-handle manner.

In the 54 medial cartilage cases, 30 showed an anterior bucket-handle tear, 16 a posterior longitudinal tear, 6 a transverse tear at the level of the medial collateral ligament and 2 showed what is really an exaggeration of the bucket-handle tear—that is, a detachment of the cartilage from its peripheral attachment. All the cases of posterior-longitudinal tear gave a rather vague history, as has already been mentioned. The original injury was not of great severity, and subsequently the joint was unstable and liable to give way on exertion. At operation it has been found that a posterior longitudinal type of tear is often not seen until the cartilage has been removed in part. Therefore on opening the knee joint the cartilage appears healthy.

Whenever the clinical diagnosis of injury to the cartilage has been clearly established, although the cartilage may appear normal on opening the joint, its removal is proceeded with and the posterior longitudinal tear will then become evident. In only one case was a normal cartilage removed.

Operative Accidents.—In one case a tourniquet paralysis was caused. This is an annoying complication, for it delays recovery considerably; but, at the same time, it is a rather disturbing one, for the tourniquet in all cases has been applied by one of two people. The tourniquet is of the rubber tube type and is applied in the same way on each occasion.

In 5 cases a sudden severe effusion developed into the joint 10 to 14 days after operation and was associated with a rise of temperature to as high as 100°. In the first three cases in which this occurred the joint was aspirated and clear fluid withdrawn. The fluid was examined and contained no pus cells and no organisms. In each of these cases treatment was by skin traction of 7 lb. on a Thomas' splint. The effusion settled within four or five days and no ill after-effects were noted. In the last two cases in which this complication has occurred aspiration was not undertaken, but the treatment by traction on a Thomas' splint was instituted with a rapid re-absorption of the fluid. No clear explanation for this complication was found. Occurring at such a late date after operation infection did not seem to be a likely cause, and in any case the fluid was sterile.

In one case a knife-blade was broken in the joint. It slipped into the posterior part of the joint, and as the tourniquet was not fully efficient and the view was obscured by blood, the joint was closed and at a subsequent date the portion of blade, having been carefully localised by X-rays, was removed. In 4 cases of posterior longitudinal tears where the cartilage was difficult to expose, the cartilage has been removed through two incisions.

Post-operative Treatment.—Following operation the knee is enclosed in a dressing of a considerable quantity of wool and a very firm bandage, and is left undisturbed until the stitches are removed on the eighth day. No posterior splint is used. On the removal of the stitches it is customary to find an effusion into the joint. This is not a tense effusion, but there is clearly fluid present.

Post-operative Physiotherapy.—John Hilton in his lectures " On Rest and Pain " observed : " The operation does not cure ; it only makes recovery possible, where, without the aid of the hand or head of the surgeon, Nature would have ceased her competition with the results of the injury or succumbed to the exhausting influence of disease." Physiotherapy is of paramount importance, and the success of the operation depends on the care with which this treatment is carried out. No treatment is commenced until the eighth post-operative day, when the stitches are removed. The knee is then given radiant heat which affords the patient a good deal of comfort, and voluntary move-

ments of the ankle, knee and hip joints are carried out. Special care is taken of the contractions of the quadriceps muscles. This treatment is carried out daily under supervision, and the patient is instructed to contract the quadriceps muscle several times a day. When the patient is able to lift the limb off the bed with the knee straight, he is allowed out of bed.

The delay in the institution of physio-therapy until the eighth post-operative day has been found advisable as the number of cases developing a considerable effusion into the joint is reduced. If the treatment is pressed on too rapidly at this stage effusion occurs and the condition of the joint and of the quadriceps deteriorates. By the twelfth to fourteenth post-operative day the patient is taken to the physio-therapy department in a wheeled chair, and in addition is allowed up in the ward for a short time. Treatment in the department consists of short-wave diathermy to the knee joint and Faradic stimulation of the muscles of the thigh. This is followed by massage. Walking exercises are given so as to prevent his developing any bad habits at this stage which will delay his recovery. Apart from educating him to walk normally he is given knee bracing exercises and tip-toe walking.

About the third week more difficult exercises are given. Heel raising and knee bending, goose step, balancing on one foot and then on the other, running up and down stairs, kneeling and sitting back on the heels. Twice a day during this time the patient is encouraged to take tours of the hospital entailing flights of stairs. He is discharged from hospital a month after operation.

After leaving hospital the patient is asked to continue exercises at home, to take daily walks of increasing length, ultimately riding a bicycle.

Observation is kept for the development of effusion into the joint and, should it appear, the patient is kept in bed until it has subsided. On leaving hospital he is warned that swelling of the knee will be a sign that he is doing too much.

As will be seen, the patient is kept in hospital for a month after the operation. This rather prolonged period has been found to be well worth while, for at the end of that time the knee is so far recovered that it can be used freely by the patient. When the patient is kept in for a shorter period he is apt to develop effusion into the joint, with corresponding failure in recovery.

The best indication of the recovery of the joint is the recovery of tone and bulk of the quadriceps muscle of the thigh, and the patient is not encouraged to return to work of any sort until the two thighs are almost equal in circumference and of equal consistence. The appearance of an effusion into the joint during the post-operative period was always associated with delay in the recovery of the quadriceps muscle. So few patients have attended a rehabilitation centre that no information is available as to the results of treatment

obtained. The miner is an individualist and does not appreciate his treatment being given to him in a large class.

The Recovery Rate.—Out of the 60 cases, 54 were injuries of the medial cartilage. Of these, 39 cases—that is 73 per cent.—were able to return to work within $4\frac{1}{2}$ months of the operation. Usually they were able to start light work two or three weeks before returning to their former work below ground, and during this time they gave the knee a test and when they found that it stood up to work, they were prepared to return below ground. In 3 cases a return to full work took place $2\frac{1}{2}$ months from the time of operation. The ages of these three patients were respectively 48, 38 and 36. The knee joints of the eldest patient showed some osteo-arthritis.

In 11 cases the return to work took place 3 months from the day of operation; in 9 cases $3\frac{1}{2}$ months, in 6 cases 4 months and in 10 cases $4\frac{1}{2}$ months.

Taking these 39 cases as being cases showing full recovery, they represent 73 per cent. of the group, and this figure corresponds very closely with Henderson's series where he found full recovery and complete relief of symptoms in 77·3 per cent. of cases, and with Duthie's 80 per cent.

Considering these cases as being the straightforward group, it is interesting to see whether there is any factor which decides the variation in the periods of disability. In the $2\frac{1}{2}$ month group their ages were 48, 38 and 36. In the patient of 48, symptoms were present for 3 years before operation; in the patient aged 38, for 5 years, and in the patient aged 36 for 2 months.

In the group returning to work within $2\frac{1}{2}$ to 3 months of operation —that is, in 11 cases—5 of the cases gave histories of symptoms of 3 months or less—5 gave histories of symptoms for from 3 to 8 months, and 1 gave a history of symptoms dating back for 5 years following an injury at football.

Of the group returning to work within $3\frac{1}{2}$ to 4 months after operation all showed symptoms appearing from 6 weeks to 6 months prior to operation.

In the group returning to work within 4 to $4\frac{1}{2}$ months of operation all showed symptoms for only 6 months before operation, except 1 case where the symptoms had been present for one year.

From these figures it would appear that the duration of symptoms before operation has little to do with the period of disability after operation. This finding does not bear out Duthie and MacLeod's conclusion that when symptoms had been present for more than two years the period of disability was likely to be longer.

In Duthie and MacLeod's cases in soldiers, full return to duty took place on an average 82 days from the date of operation. The average age of their patients was $25\frac{1}{2}$ years. Terhune and others followed 70 cases, and in their group of cases of injury to the medial meniscus the average period of disability was only 50 days from the

time of operation. These writers also noted that the period of disability was directly related to the duration of symptoms before operation —the longer the duration of symptoms the longer the period of disability.

In Hamilton and Finkelstein's series of 103 cases of damage to the medial cartilage in soldiers, the average period of disability was 49 days from the time of operation. Bristow's view was that a case of cartilage injury should be able to resume games in 6 to 8 weeks from the time of operation.

Malkin in his series of 86 cases of medial cartilage injuries in soldiers found that 81 per cent. were fit to resume full soldiering duties in 6 to 9 weeks from the day of operation, and eventually 82 out of the 86 cases were able to resume full duties.

My results make poor reading in contrast with these series of cases, but that may be explained in part by the increased age of my cases and the arduous work to which miners have to return.

In the remaining 15 cases in this series of medial cartilage injuries, 10 returned to work within 10 months; 2 cases returned to work 5 and $6\frac{1}{2}$ months respectively after operation. Their ages were 35 and 31 years, and in each case the joint showed no evidence of any osteo-arthritis. This delay was due to the presence of an effusion which persisted. Ultimate recovery was full, and no satisfactory explanation for the effusion was found. They have continued at work for the past 18 months without further trouble.

In 1 case 7 months elapsed due to the patient developing a neuroma in the divided infra-patellar branch of the saphenous nerve. This was the only case of injury to this nerve. The delay in return to work was understandable when one remembers the amount of kneeling a miner has to do, and any pain or discomfort in the knee will be a valid reason for his failing to return to work. Without any treatment the condition cleared up satisfactorily.

In another case 7 months elapsed due to the patient having developed a pulmonary embolism following operation. This was the only case of post-operative pulmonary complication that occurred.

In 4 cases 6 to 9 months' disability occurred in patients who were over 50 years of age. An obvious degree of osteo-arthritis was present in the joints. Eventually they returned to work and have been at work for the past two years without trouble It is questionable whether operation should be carried out in such cases; yet when the patient is unable to work on account of the cartilage injury, one is unwilling to deny him the chance of resuming work even after being off for 6 to 9 months. Where the evidence of cartilage injury is clear cut, and where, as a result, the symptoms of locking are so severe as to prevent the man working, then I think operation is justified. It is possible that a rest of 9 months would allow of his returning to work in any case.

In 4 cases there was no return to work as underground workers.

The cause of failure to recover in these cases was : one patient had suffered injury to the crucial ligaments before operation. Subsequently he suffered a further injury to the knee while convalescing from the operation for removal of the medial cartilage. His knee became quite unstable and eventually an arthodesis of the joint was carried out. His original time in hospital was only 15 days, and if he had remained longer until the knee was stronger, his subsequent history might have been different.

In 1 case there was an associated injury of the ankle and an old fracture of the leg. The remaining 2 cases drifted away from the mines and were employed eventually in different occupations, which they were able to do satisfactorily.

Thus of the cases of injury to the medial cartilage, 49 out of the 54 cases returned to work below ground within 10 months of operation. This represents a percentage recovery rate of 90. Selection of cases here plays an important part, for with proper choice of cases 100 per cent. should return.

Factors contraindicating Operation.—(1) *Associated injuries*—crucial and collateral ligament injury. In civil life a knee cage would allow use of the limb, but a miner could not work with such a device. (2) Very gross osteo-arthritis. (3) Laxity of the ligaments is not a contra-indication, for with complete restoration of power of quadriceps, stability of the joint can be assured. There is difficulty in assessing how much lateral or antero-posterior mobility can be made good by the quadriceps muscles, and it is these cases which probably prevent 100 per cent. recovery rate.

Of the cases of injury to the lateral cartilage there were in all 6 cases. In 2 of these the pathological condition was a congenital disc cartilage. The ages of these 2 patients were respectively 32 and 21 years. In the younger patient he had had trouble with the knee since the age of 11 years, when there developed a loud crack in the joint on movement following a mild injury. He had continued at school and later at work until the age of 21 when, following an injury in the pit, the joint became swollen and he had to stop work. The whole cartilage was removed at operation.

The second patient, aged 32 years, developed a crack in the joint on movement following an injury 4 months previously. In this case the whole cartilage was removed.

In both cases the joint was healthy from the radiological point of view, and return to full work took place 4 months after operation.

In the remaining 4 cases of injury to the lateral cartilage there was a tear of the anterior bucket-handle type, and symptoms had been present for from 7 to 10 months before operation. This delay in seeking treatment is largely due to the doubt as to the diagnosis. The condition is rare, and in consequence there is a natural unwilling-ness for the diagnosis to be made.

All the patients were in the same age group, their ages being

36, 36, 35 and 34. Radiologically the joints were healthy, and at operation the whole cartilage was removed. In 2 cases two incisions were used, one anteriorly for the freeing of the anterior part of the cartilage and one posteriorly for the removal of the posterior part. The necessity for the two incisions is questionable and may well be due to inexperience in dealing with lateral cartilages. In each case the recovery was slow and was delayed by the presence of a persistent effusion, with corresponding delay in the recovery of the quadriceps muscle. In each case return to work occurred, but only after a period of $6\frac{1}{2}$ months.

This delay in recovery of cases of lateral cartilage injury has been noted by all observers. In Terhune's series 71 days were required for these cases as compared with 50 days for the medial cartilages, and in my series $6\frac{1}{2}$ months as compared with $4\frac{1}{2}$ months for the best of the cases of medial cartilage injury.

CONCLUSIONS

Sixty cases have been described in some detail, the series consisting of 54 injuries of the medial cartilage and 6 of the lateral.

Of the 60 cases all but 4 were able to resume work as underground mine workers.

The period of disability for medial cartilage injuries was shorter than for lateral cartilage cases, taking into account the age of the patient and the condition of the joint.

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NEW BOOKS

Active Psychotherapy. By ALEXANDER HERZBERG, M.D. Pp 152. London: William Heinemann. 1945. Price 12s. 6d. net.

The author has written this book with the object of describing a short method of psychological treatment which he believes is greatly needed. The method he advocates is an integration of psychoanalysis, persuasion, and the practical arrangement of the person's life. But such a combination is not original or new; it is the method which every practising psychiatrist utilises. There is no real justification for a book of this type; it could not be recommended to the undergraduate, and there is nothing in it which every psychiatrist does not know.

Aviation Neuro-Psychiatry. By R. K. IRONSIDE, M.B., F.R.C.P., and I. R. C. BATCHELOR, M.B. Pp. 167. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 8s. 6d. net.

This is an interesting book, based on first-hand experience, which studies the psychological problems of air-crews. It treats of the man in relation to the special environment which he has chosen. We are told how persons may be selected for flying, how confidence may be developed, and how the various forms of neuro-psychiatric disturbance which are prone to develop may be recognised. Many case records are detailed. It is gratifying to see so much emphasis placed on prophylaxis. This is a book which in subsequent editions might be considerably enlarged, but in the meantime it will serve a useful purpose.

A Class Book of Practical Embryology for Medical Students. By P. N. B. ODGERS Pp. 63, with 30 illustrations. London: Oxford University Press. 1945 Price 7s. 6d.

Dr Odger's new book is essentially a laboratory atlas and contains a series o line drawings, twenty-seven in all, of sections of pig embryos of 6 to 10 mm. Th illustrations occupy the right-hand page of the opened book and on the facing pag there is a short descriptive text. The line drawings are clearly produced in simpl black and white and are of sufficient magnification to make the individuality of th various structures easily recognised.

In the drawings only the more obvious or most important structures have bee featured and these are all fully labelled. There might be some difference of opinio on the advisability of such a complete system of labelling.

The book is pleasingly produced and should prove a useful companion to systematic textbook in the study of practical embryology.

What People Are. A Study of Normal Young Men. By C. W. HEATH an Collaborators. Pp. xvi+141. London: Oxford University Press. 194! Price $2.00.

This is an account of a study carried out by a team of experts working unde the Grant Trust. The purpose was to examine the characteristics shown by group of apparently normal people. The subjects chosen were undergraduates a Harvard who showed no apparent abnormality. " Normal " the authors define a the balanced harmonious blending of functions that produce good integration; an a normal individual is a balanced person whose combination of traits of all sor allows him to function effectively in a variety of ways. The work is the result collaboration between an internist, a psychologist, a psychiatrist, a physiologist, a anthropologist and a personal worker, and it covers many fields of investigatio The authors have found it difficult to achieve a practical grasp of the " whole person, though they consider that this may eventually be possible. At present the analys

of factors which make for health and successful functioning in spite of variability of characteristics represents an immense field of work and much remains to be done.

A Short Anglo-Polish Medical Dictionary. By W. TOMASZEWSKI, M.D. Pp. 164. Edinburgh : E. & S. Livingstone Ltd. 1945. Price 8s. 6d.

This little work contains a fairly extensive list of English medical terms arranged alphabetically and gives their Polish equivalents. Various appendices supply supplementary information on common contractions, weights and measures, medical schools and common bedside phrases. A series of eight plates illustrates surgical instruments and laboratory apparatus.

A creditable production which should be of the greatest value to our Polish allies who for some considerable time may have to depend on textbooks written in English.

The History of Surgical Anæsthesia. By THOMAS E. KEYS. Pp. xxx+191, with 45 illustrations. New York : Schuman's. 1945. Price $6.00.

This fascinating story is traced back to primitive times and through the Middle Ages to the early 19th century when modern methods began to appear. The history of ether anæsthesia is very fully recorded, but chloroform receives rather scant notice, and as might be expected the developments of the present century demand a great deal of attention. Numerous illustrations have been culled from the older books and there are some excellent portraits of pioneers in this field. A curious feature of the book is the wealth of references offered to the student of history and the tables of significant events in chronological sequence. A concluding chapter contains an essay by Dr Noel A. Gillespie on the future of anæsthesia.

The book is excellently written and beautifully produced and should become the treasured possession of many.

NEW EDITIONS

The Infant. A Handbook of Management. By W. J. PEARSON, D.M., F.R.C.P., and A. G. WATKINS, B.SC., M.D., F.R.C.P. Third Edition. Pp. vii+60. London : H. K. Lewis & Co. Ltd. 1945.

This little book sets out the broad facts of growth and development in infants and children ; of breast and bottle feeding ; and of the care and management of premature babies. It also gives details of diets, and of caloric requirements at various ages ; and supplies information about vitamins, their natural sources in foods, and their appropriate dosage in their concentrated forms. In a further section recipes for the making up of special milk preparations and of other special foods are given ; and a useful list of prescriptions in common use is supplied.

The book can be recommended as a trustworthy guide to mothers, and nurses who have not received special training ; and for trained nurses or general practitioners it is a useful little book of reference.

A Text-book of Surgical Pathology. By CHARLES F. W. ILLINGWORTH, M.D., CH.M., F.R.C.S. EDIN., and BRUCE M. DICK, M.B., F.R.C.S. EDIN. Fifth Edition. Pp. viii+728, with 306 illustrations. London : J. & A. Churchill Ltd. 1945. Price 42s. net.

In this new edition many alterations and additions have been made to bring the text into accord with current opinion. The sections on surgical shock and burns have been re-written and the chapter dealing with anærobic infection of wounds has been revised to bring it into line with the experience gained in the present war. The book can be thoroughly recommended for both graduates and senior students.

The Pathology of Internal Diseases. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. EDIN., F.R.C.P. LOND., DIPL.PSYCH., F.R.S.C. Fourth Edition. Pp. 857, with 366 illustrations and 8 coloured plates. London: Henry Kimpton. 1945. Price 50s. net.

This text-book is written primarily for the physician and is in reality an illustrated text-book of medicine, each pathological process being correlated with the clinical manifestations of the disease. In this new edition many sections have been added and others re-written because of the advances made in our knowledge of pathological processes. Primary atypical pneumonia, alloxan diabetes and dietary cirrhosis of the liver are but a few of the topics discussed. This excellent work will give the physician a sound understanding of pathology and thus enable him to visualise disease in all its forms.

A Manual of Zoology. By L. A. BORRADAILE, SC.D. Eleventh Edition. Pp. xiii+813, with 551 illustrations. London: Oxford University Press. 1945. Price 24s. net.

This well-known text-book, familiar to many Edinburgh students, has been revised and improved in several ways. Various notes of functional interest have been added, such as those on water-regulation and on the walking of vertebrates, and here and there comparative comments have been inserted, e.g. to indicate the evolutionary importance of the reptiles, which help to give a fuller picture of animal progress. A new description of the maturation of the germ-cells includes excellent diagrams of the stages in reduction division and in crossing over. In all, the new contributions have added 63 pages and 32 diagrams to the volume. The new glossy paper, almost luxurious for war-time production, has enhanced the quality of many of the illustrations.

BOOKS RECEIVED

BECKMAN, HARRY, M.D. Treatment in General Practice. Fifth Edition. Reset   .   .   .   .   .   .   (*W. B. Saunders Co., London*)   50s. net.

BOYD, MARK F., M.D., M.S., C.P.H. Preventive Medicine. Seventh Edition. Revised   .   .   .   .   .   (*W. B. Saunders Co., London*)   27s. 6d. net.

BROWN, RAMSAY, C.A. Guide to Medical Practices.
(*H. K. Lewis & Co. Ltd., London*)   5s. net.

BULBULIAN, ARTHUR H., M.S., D.D.S., F.A.C.D. Facial Prosthesis.
(*W. B. Saunders Co., London*)   25s. net.

CANTAROW, ABRAHAM, M.D., and MAX TRUMPER, PH.D. Clinical Bio-chemistry. Third Edition, Revised   .   (*W. B. Saunders Co., London*)   32s. 6d. net.

DARLING, H. C. RUTHERFORD, M.D., M.S., F.R.C.S., F.R.F.P.S. Surgical Nursing and After-Treatment. Ninth Edition.
(*J. & A. Churchill Ltd., London*)   12s. 6d. net.

DREW, LILLIAN CURTIS. Individual Gymnastics. A Handbook of Corrective and Remedial Gymnastics. Fifth Edition revised and edited by HAZEL L. KINZLY   .   .   .   .   .   .   (*Henry Kimpton, London*)   15s. net.

GIFFORD, SANFORD R., M.A., M.D., F.A.C.S. A Textbook of Ophthalmology. Third Edition, Revised   .   .   .   (*W. B. Saunders Co., London*)   20s. net.

GLENDENING, LOGAN, M.D., and EDWARD H. HASHINGER, A.B., M.D. Methods of Treatment. Eighth Edition, Revised   .   (*Henry Kimpton, London*)   50s. net.

HIRSCH, EDWIN W., B.S., M.D. Woman's Inner Secret.
(*Research Publications, Chicago*)   ...

MAJOR, RALPH H., M.D. Physical Diagnosis. Third Edition, Revised.
(*W. B. Saunders Co., London*)   25s. net.

MOORHEAD, JOHN J., B.S., M.D., D.SC., F.A.C.S. (D.S.M.) Clinical Traumatic Surgery   .   .   .   .   .   (*W. B. Saunders Co., London*)   50s. net.

POTTENGER, FRANCIS MARION, A.M., M.D., LL.D., F.A.C.P. Symptoms of Visceral Disease. Sixth Edition   .   .   (*Henry Kimpton, London*)   25s. net.

TRAIL, RICHARD R., M.C., M.A., M.D., F.R.C.P. Chest Examination. The Correlation of Physical and X-ray Findings in Diseases of the Lung. Second Edition   .   .   .   .   (*J. & A. Churchill Ltd., London*)   12s. 6d. net.

WHITE, MARGARET MOORE, M.D., F.R.C.S., M.R.C.O.G. The Symptomatic Diagnosis and Treatment of Gynaecological Disorders. Second Edition.
(*H. K. Lewis & Co. Ltd., London*)   16s. net.

INCREASING INCIDENCE OF PULMONARY TUBERCULOSIS IN CHILDREN IN GLASGOW *

By STUART LAIDLAW

From the Public Health Department, Glasgow

ONE feature which has been noticeable recently with regard to the rising incidence of pulmonary tuberculosis in Glasgow is that the increase is not confined to adults, and that the number of children under fifteen years of age suffering from pulmonary tuberculosis is definitely increasing. This is all the more evident as the non-pulmonary forms of tuberculosis do not show a proportionate increase, with the single exception of meningeal tuberculosis which has increased by 80 per cent. over pre-war figures.

In order to ascertain the extent of this increase, we extracted the number of cases notified to the Public Health Department during 1943, and compared them both in type and distribution with the cases notified during 1938, a typical pre-war year. The results showed that, whereas during 1938 the Department received 233 notifications, 453 were received during 1943, an increase of 94 per cent. The age and sex distributions of the notifications did not differ materially in the two groups ; neither did we find that the type of disease had shown any material change. It has been customary to divide the notified pulmonary cases into three groups :—

> Group 1 : Cases of enlarged hilar glands where there may be, in addition, a minimal pulmonary lesion.
> Group 2 : Cases which show major involvement of one lung or less extensive lesions of both lungs.
> Group 3 : Cases where the disease extends throughout the greater part of both lungs or is miliary in type.

It was found that in 1943 approximately one-third of the patients under fifteen years of age fell into each of these groups, with perhaps a few more in category 1 than in category 2 or category 3. This distribution was very similar to that prevailing in 1938 and did not

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* Read at a meeting of the Tuberculosis Society of Scotland, held in Glasgow on 20th October 1944.

vary materially in either sex. It would appear, therefore, that the severity of the infection among children has not increased in the individual case, although the number of cases has nearly doubled.

What is the reason for this? Investigation shows that whereas in 1938, 18 per cent. were found to be definite contacts with a case of open pulmonary tuberculosis in the home, 32 per cent. now show that relationship. Contact infection, therefore, is evidently a considerable contributory factor in the present increase. This is not surprising when it is realised that a dearth of hospital beds means delay in the admission of infectious cases to institutions and the retention of large numbers of chronic cases under domiciliary treatment, a proportion of whom would be in institutions in normal times.

Examination of the addresses of the children notified convinced us that some areas of the city were recording an unduly large number of cases, and it was with the object of finding some statistical support for this feature that we drew up a comparison of the five Public Health Divisions in Glasgow. These divisions were first classified according to the number of overcrowded houses per 1000 of the general population. A comparative factor for each division was thus obtained. Next, the number of children under fifteen years of age resident in each division was ascertained, and when this figure was weighed against the number of cases of pulmonary tuberculosis in children notified during 1943 from that particular area, it was possible to arrive at the sickening rate per 10,000 children resident there. The results obtained are best illustrated by a simple table.

Area.	No. of Overcrowded Houses per 1000 of the General Population.	Sickening Rate from Pulmonary Tuberculosis per 10,000 Children.
1	98	22·6
2	78	16·6
3	67	14·8
4	62	16·6
5	51	13·6

This shows that the sickening rate is highest where overcrowding is worst, and in addition a study of the clinical conditions of the individual patients showed that the disease tended to throw up the more severe types (Group 3) in larger proportion where the overcrowding was greatest. The policy of the Public Health Department, by which every endeavour is made to rehouse tuberculous families living under overcrowded conditions, results in a transference of infected persons from the more overcrowded to the less overcrowded areas. The result of this policy is that children in new housing schemes sicken from tuberculosis which was originally contracted in slum areas.

It is difficult to assess what additional features are playing a part in this increase. For example, although Government circles are emphatic that the nation's diet has been adequate, it is obvious that most children nowadays get far less fresh fruit, fats and sugars than

they had in pre-war days, despite the larger incomes which many families are now receiving.

When one notes that (1) non-pulmonary tuberculosis has not increased to a comparable extent with pulmonary tuberculosis (excepting meningeal forms of the disease), (2) the average severity of the individual case has not increased, and (3) a very much larger proportion of the cases are attributable to contact infection, it is obvious that the solution of the problem must lie in improved isolation, and this can only be obtained by the early removal of infectious cases to hospital and by an improvement in the housing conditions, in order that young children should not be exposed to repeated and massive doses of infection.

Although the notification rate for pulmonary tuberculosis in Glasgow has risen from an average of 1650 cases per annum for the years 1934-39, to 2750 cases for the years 1943-44, the death-rate has only risen from 1000 per annum to just over 1100 per annum, and it is very difficult to understand why this is so. It certainly cannot be due to better medical attention as there is a shortage of doctors, nor to better nursing for the same reason. The duration of time spent in sanatorium and hospital has actually been reduced, and the food has not been of anything like the pre-war standard. One would expect under these circumstances a marked increase in mortality instead of a decrease.

I intend leaving this question to the Society as a topic for discussion and comment.

SOME EXPERIENCES IN MASS RADIOGRAPHY *

By ALEX. MACLEAN

From Glasgow Mass Radiography Unit

MASS miniature radiography of the civilian population has been in operation in Glasgow since May 1944, but, while some 6000 persons have passed through the Unit, work on the whole has been on an experimental basis and the Unit is only now emerging from its initial trial period.   The figures quoted are small, and beyond saying that the results on the whole are comparable with those found elsewhere, the findings will not be discussed.

A mass radiography unit may work at a centre or may work in industrial premises.   Its best work will naturally be produced under the former circumstances and, further, a centre is necessary for the storage of records and as headquarters.   On the other hand, a considerable upheaval will be caused in works which have many employees if the workers all travel to a distant centre for X-ray examination, and it is better that the unit should set up and operate at a suitable point in such works.   The dividing line between operations at a centre and operations on industrial premises is not easily decided, but it is unlikely that the Unit will travel to any workplaces which cannot provide at least 2000 volunteers for examination or, in other words, a fortnight's work.   It is obvious, therefore, that administration is of great importance in such a unit, and the rest of this talk will be devoted to administrative problems.

The staff of the Glasgow Mass Radiography Unit consists of medical, technical and clerical sections.   The Medical Director is in charge of the Unit and is responsible to the Senior Assistant Medical Officer for Tuberculosis and, through him, to the Medical Officer of Health ; he should have experience of both clinical tuberculosis and of chest radiology ; he must have access to the services of a consultant radiologist, of a bacteriologist and of a throat specialist ; observation beds in hospital should be at his disposal ; he should co-operate as much as possible with his fellow tuberculosis officers and, in particular, with the tuberculosis officer in whose area he is operating for the time being.   The technical staff comprises a senior radiographer, a junior radiographer and a dark-room technician, but increase of this staff by the appointment of another junior radiographer is under contemplation.   The clerical staff is at present four in number, but the senior clerk has developed into a combination of organising secretary and of liaison officer between the Unit and industry ; the

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* Introduction to a demonstration to the Tuberculosis Society of Scotland, held in Glasgow on 20th October 1944.

keeping of statistics has become of great importance, and the Unit has to deal with a considerable volume of correspondence, with the result that an increase of clerical staff to the number of six is imperative ; it is thought that this number will enable the clerical staff also to cover the post of marshaller which up till the present has been taken by First Aid Post staff.

Protection of the staff from the deleterious effects of X-rays is of great importance. At the centre, the X-ray room is adequately lead-lined, and only the technical staff need be considered in this respect, but on industrial premises all staff come in contact with the rays. Staff exposed to the rays should wear dental films as a check on over-exposure and have regular blood tests done.

Mass radiography is a service for the examination of the public, with the intention of detecting unsuspected disease at as early a stage as possible in the development of that disease. Not only will tuberculosis of the lungs be found, but also inflammatory and neoplastic conditions and abnormalities of the heart and large vessels. The mass radiography unit may make contact with the public through employers or workers' representatives seeking examination of their workers or from itself sending invitations to such people. The sympathy of employers' organisations and of trade unions has already been elicited on a national basis by the Government, but individual units are left to make suitable arrangements locally ; the important thing to remember is that both management and workers must be consulted before the examination of employees takes place, and it is well for the initial approach to be made at least eight weeks before examinations begin. Intensive propaganda will be necessary to convince the prospective examinees of the desirability of submitting to the investigation, and in this connection the press, the radio, the cinema, leaflets and posters should all play a part.

The primary object of mass radiography is the detection of tuberculosis, and it is therefore fitting that a mass radiography unit should dovetail with its local authority's tuberculosis scheme. In Glasgow, it has developed in such a way that the unit undertakes the observation of cases of doubtful diagnosis or, where tuberculosis is noted, of cases of doubtful activity and presents the tuberculosis dispensary and hospital, if possible, with a completed case. The patient's doctor is informed of such abnormalities as are found and of the action taken, and where non-tuberculous disease is concerned the further observation and treatment of the case is generally left to him.

Mass radiography, unlike ordinary tuberculosis administration which is based on the patient's place of residence being situated in the local authority's area, is administered according to the place of employment of the person examined. Normally a proportion of persons employed in any area will be resident outside that area and treatment will still be the responsibility of the area in which the residence

is placed. If tuberculosis is detected in a person resident in such an area the local authority of that area and the person's doctor will both be informed.

The findings are regarded as strictly confidential and are not divulged except with the examinee's consent. In this respect, the information cannot even be communicated to the private doctor unless the individual divulges his name and gives permission for him to be told. The works doctor is not told nor, of course, is the management.

It is probable that before undertaking mass surveys of the population a certain amount of planning will be necessary. It is of particular importance to examine as many as possible of the age-groups in each sex which are known to produce most pulmonary tuberculosis—thus pulmonary tuberculosis among Glasgow residents in the last few years has been greatest in both sexes in persons aged from sixteen years to thirty years, with a further prevalence in men about the age of forty years. The experience of the Unit so far has been that females in the dangerous age-groups and the men about forty have been turning up well, but not men from eighteen to thirty —these latter have, however, been surveyed by mass radiography in the Services, and individuals found to have tuberculosis have been referred to their home areas for treatment. Again, certain occupations are more dangerous from the point of view of association with tuber-culosis than others. In the past most of the work has been on clerical and administrative workers who, of course, have produced tuberculous patients like the rest of the population, but it is intended in the future to concentrate more on those working in unsatisfactory working conditions—for example, in the immediate future, clothing workers.

DEMONSTRATION.—The Society then saw a demonstration in the methods of mass radiography. Some of the personnel of a large employing authority were photographed. The methods of pro-jecting and recording results were examined. Large photographs of those recalled for further examination were also demonstrated.

THE PATHOGENESIS OF TUBERCULOUS EPIDIDYMITIS *

By WALTER M. BORTHWICK, M.B., CH.M.

From Robroyston Hospital, Glasgow

INTRODUCTION

To judge from the arguments and discussions which have appeared in the medical press, the problem of the spread of the tubercle bacillus to the epididymis has not been solved to the satisfaction of all who are interested in this subject. For many years two opposing schools of thought have been propounded, one led by Barney [1] who believes that the primary genital lesion is in the epididymis, while the second, the greatest advocate of which is Young, [2] holds the view that the primary genital lesion is in the seminal vesicles and prostate, the epididymis becoming secondarily infected. To myself, having read the results of investigations by these two workers, the problem persisted and it seemed that the proper procedure was to investigate all the cases of male genital tuberculosis at my disposal, in an attempt to clarify the position at least in my own mind.

Since the problem before the Society is the pathogenesis of tuberculous epididymitis, I hope you will forgive me if I omit much of the information I collected from the cases studied. Lastly, I would like to point out that the study did not rely entirely on hospital case records but included past patients and all those who, for the purpose of this investigation, came under my nominal charge.

GENERAL INCIDENCE OF TUBERCULOUS EPIDIDYMITIS.—The material used for this study consisted of case-records of male patients admitted to Robroyston Hospital between the years 1921 and 1941 inclusive. During these twenty-one years there were 5476 males of all ages admitted to hospital suffering from tuberculosis in one or more of its forms. From that total 402 case histories (7·3 %) were extracted which recorded the occurrence of involvement of the epididymis by tuberculosis, whether or not that was the cause of admission to hospital.

At first sight, study of Table I gives the impression that genital tuberculosis has become much more frequent. That is partly due, however, to the fact that a genito-urinary department was created in Robroyston Hospital in 1933 and a visiting urologist appointed. Many of the admissions from that date had been examined previously by the urologist and had been recommended for admission to the hospital.

In addition, the fact that such a department existed attracted patients from districts outwith the Glasgow area and accounted in no little measure for the increase in genital cases. Probably the nearest approach to the true incidence figure must lie in the averages of the years prior to 1934. On this basis a figure of 4·5% is reached, which corresponds closely to the figure of 5% given by Barney and Colby [3] and 4·7% found by Miller and Lustock.[4]

TABLE I

Yearly Percentage Incidence of Patients in Robroyston Hospital Suffering from Tuberculous Epididymitis

Year.	Total Number of Male Admissions.	Number of Epididymitis Cases.	Percentage.	Year.	Total Number of Male Admissions.	Number of Epididymitis Cases.	Percentage.
1921	367	1	0·3	1932	245	23	9·4
1922	376	6	1·6	1933	205	24	11·7
1923	408	10	2·5	1934	209	36	17·2
1924	365	10	2·7	1935	227	31	13·7
1925	263	4	1·5	1936	244	25	10·3
1926	362	9	2·5	1937	211	32	15·2
1927	279	13	4·7	1938	211	26	12·3
1928	247	18	7·3	1939	168	32	19·1
1929	237	16	6·8	1940	137	21	15·3
1930	222	18	8·1	1941	220	25	11·4
1931	273	22	8·1	...	...	...	...

AGE INCIDENCE.—The youngest patient in the series was eight months old, while the oldest was sixty-three years of age. The percentage incidence in the various age groups can be seen by reference to Table II.

TABLE II

Age Distribution of 402 Cases of Tuberculous Epididymitis

Age Groups (in Years).	Number of Cases.	Percentage.	Age Groups (in Years).	Number of Cases.	Percentage.
0-5	12	3·0	36-40	34	8·5
6-10	4	1·0	41-45	35	8·7
11-15	12	3·0	46-50	18	4·5
16-20	46	11·6	51-55	16	4·0
21-25	76	19·1	56-60	13·	3·2
26-30	78	19·4	61-65	6	0·7
31-35	52	12·9	...	...	...

The outstanding conclusion to be drawn from this section, one that has been stressed by numerous writers including Thomson-Walker,[5] Robinson [6] and Schultz,[7] is that male genital tuberculosis occurs most commonly during the years of maximal sexual activity.

The largest series of cases found by the writer in a study of the available literature was that of Sjöstrand,[8] who collected 509 cases

from several sources and calculated the age incidence. The results of Sjöstrand, Keyes,[9] Kretschmer[10] and the present series are compared in Table III.

TABLE III

Age Incidence of Tuberculous Epididymitis

Investigator.	Number of Cases.	Age Groups.	Percentage.	Age Groups.	Percentage.
Sjöstrand	509 (Collected)	15-39	70	20-39	63
Keyes	100	15-39	73	20-39	65
Kretschmer	94	...	...	20-39	71
Present writer	402	16-40	71	21-40	60

EXTRA-GENITAL TUBERCULOSIS.—In the 402 men, at least one extra-genital tuberculous lesion was proved in 355 (88·3%). In the remaining 47 (11·7%) cases, routine X-ray of the chest was not carried out and the urine was not tested biologically for the presence of organisms.

INJURY AS A PRE-DISPOSING FACTOR.—In the present series, injury appeared to have little influence in the production or localisation of the genital disease. Only 18 patients attributed their lesion to injury, and 12 of these men asserted that the local lesion occurred immediately after the injury. In the remaining 6 cases, the intervals between the onset of genital disease and trauma were one month in 2 cases, two, three and six months respectively in 3 cases and one and a half years in the remaining case.

Similarly, I concluded that gonococcal epididymitis had little or no influence on the occurrence of tuberculous epididymitis as only 10 men (2·4%) gave a history of previous infection of the epididymis by the gonococcus.

THE LOCAL LESION

The epididymitis was unilateral in 175 men (43·5%) and bilateral in 227 (56·5%). Those counted as bilateral included 41 men who were admitted with unilateral disease, but who later developed disease of the other side in hospital. Difficulty was experienced in determining the time interval between the onset of disease on the two sides in the bilateral cases, but very definite records existed of 63 patients, most of whom developed the genital disease in hospital.

TABLE IV

Interval between the Onset of Disease of the Two Epididymes in 63 Patients

Time in months	·1	·3	·6	·12	·24	·36	·72	·96	·108
Number of Cases	2	18	37	47	55	60	61	62	63
Percentage	3·2	28·6	58·7	74·6	87·3	95·2	96·8	98·4	100

In these 63 cases Table IV shows that 37 (58·7%) became bilateral within six months, while 47 (74·6%) showed recurrence within one year. There is general agreement, and the present series confirms, that the tuberculous affection of one epididymis is followed in a majority by the onset of disease on the hitherto healthy side. The spread of the disease to the second side appears to be an early feature in most cases, but may occur at any time up to a period of nine years.

PELVIC COINCIDENTAL LESIONS

Out of the total of 402 cases, 237 had one or more rectal examinations carried out while in hospital. Positive results were obtained in 207 (87·3%) of those examined rectally.

TABLE V
Number of Cases in Each Age Group

Age Groups (in Years).	Rectal Positive.	Rectal Negative.	Age Groups (in Years).	Rectal Positive.	Rectal Negative.
·5	1	—	36-40	20	4
6-10	...	1	41-45	10	1
11-15	7	1	46-50	7	1
16-20	34	4	51-55	5	2
21-25	40	8	56-60	6	1
26-30	42	4	61-65	2	...
31-35	24	3	..	...	...

TABLE VI
Comparison of Incidence of Tuberculous Epididymitis with the Incidence of Tuberculous Prostatitis and Seminal Vesiculitis

Age Groups (in Years).	Percentage Incidence of Tuberculous Epididymitis.	Percentage Incidence. Rectal Positive.	Age Groups (in Years).	Percentage Incidence of Tuberculous Epididymitis	Percentage Incidence. Rectal Positive.
·5	3·0	0·5	36-40	8·5	9·7
6-10	1·0	...	41-45	8·7	9·2
11-15	3·0	3·4	46-50	4·5	3·4
16-20	11·6	16·4	51-55	4·0	2·4
21-25	19·1	19·3	56-60	3·2	2·9
26-30	19·4	20·3	61-65	0·7	1·0
31-35	12·9	11·6	...	...	...

Study of Tables V and VI shows that tuberculosis of the prostate and seminal vesicles occurred at all ages with approximately the same frequency as was found in the age incidence of tuberculous epididymitis.

The two groups of cases were studied separately, the one in which no abnormality was found on rectal examination and the other in which pelvic genital disease was detected.

RECTAL NEGATIVE GROUP.—The number of these cases is 30 (12·7%) of those rectally examined. Twenty-four (80%) had involve-

ment of one epididymis, the frequency of right and left being the same. The duration of the unilateral epididymitis in all cases was under ten months. Bilateral epididymitis was present in 6 instances, the time period being under six months for 4 cases and two and four years respectively for the remaining 2 cases.

RECTAL POSITIVE GROUP.—This group comprises 207 cases (87·3%) of those examined rectally. For the purposes of detailed study I have divided these cases into three categories.

(a) PATIENTS WITH EPIDIDYMITIS, PROSTATITIS AND VESICULITIS ON ADMISSION.—There were 195 patients in this group. Disease of one or both seminal vesicles without palpable changes in the prostate was present 44 times, while prostatitis without vesiculitis was found in 20 patients, the remaining 131 men having disease of the prostate and seminal vesicles. These 195 patients were divided into two groups, the first showing the relationship between the disease of the epididymis and seminal vesicle and the second showing the relationship between prostatitis and epididymitis.

Epididymitis and Vesiculitis.—Of the 195 patients, 80 had unilateral epididymitis and 115 bilateral epididymitis and Table VII shows the associated genital lesions.

TABLE VII

Associated Epididymal and Seminal Vesicular Disease in 195 Men

Associated Lesions.	Number.	Associated Lesions.	Number.	Associated Lesions.	Number.
RE+R.S.V.	18	LE+L.S.V.	17	BiE+BiSV.	98
RE+L.S.V.	0	LE+R.S.V.	1	BiE+R or L.S.V.	8
RE+BiS.V.	20	LE+BiS.V.	13	BiE+No SV.	9
RE+No SV.	7	LE+No SV.	4	...	...

RE = right epididymis
BiE = bilateral epididymitis
BiSV = bilateral seminal vesiculitis.
No SV = no vesiculitis.
LE = left epididymitis
R.S.V. = right vesiculitis
L.S.V. = left vesiculitis.

It can be seen that in the total of 80 patients with unilateral epididymitis there was involvement of one seminal vesicle (with one exception always the homolateral one), in 36 (45%) involvement of both vesicles in 33 (41·3%) and no palpable vesicular disease in 11 (13·8%). Excluding these cases with no palpable prostatic disease, the duration of the epididymal lesions in the remaining patients was as follows: 13 cases (16·3%), less than one month, 44 cases (55%), less than three months and 57 cases (82·6%) less than six months. In men with unilateral epididymitis and bilateral vesiculitis, the epididymal lesion had been present for less than six months in 28 out of 33 cases (84·9%).

There were 115 patients with bilateral epididymitis, in 98 of whom (85·2%) bilateral vesiculitis was also present. The duration of the epididymal lesion in these men was less than one year in 72 (73·6%).

Epididymitis Prostatitis.—In the 80 patients with unilateral epididymitis, Table VIII, 21 (26·3%) had disease of one lateral prostatic lobe, 38 (47·5%) had disease of both lateral prostatic lobes and 21 (26·3%) had no palpable prostatic disease. The duration of the unilateral epididymitis in these patients was less than seven months in 50 (84·8%), between seven months and one year in 3 (5·1%). These results show that in most of the cases under review *the association* of epididymitis and prostatitis was an early feature. That bilateral prostatitis occurred as frequently as unilateral prostatitis in men with unilateral epididymitis in the same interval of time is shown by the following results : out of 21 cases of unilateral epididymitis and unilateral prostatitis, 18 (85·7%) showed that combination within six months of the onset of the epididymal lesion, while of 38 cases of unilateral epididymitis with bilateral prostatitis, the prostatic lesion was discovered in 32 (84·2%) within the same period from the onset of the epididymal lesion.

TABLE VIII

Associated Epididymal and Prostatic Disease in 105 Men

Associated Lesions.	Number.	Associated Lesions.	Number.	Associated Lesions.	Number.
RE+RP	11	LE+LP	10	BiE+BP	91
RE+BP	22	LE+BP	16	BiE+R or LP	1
RE+No P	10	LE+No P	11	BiE+No P	23

RP = disease right lateral prostatic lobe.   LP = disease left lateral prostatic lobe.
BP = disease both lateral prostatic lobes.   No P = no prostatic disease.

Ninety-one of the 115 patients with bilateral epididymitis (79·2%) were found to have disease in both lateral prostatic lobes. The association of bilateral prostatitis and bilateral epididymitis appeared to be an early feature, as 74·7% of the cases were found within one year of the onset of epididymitis. The figure approximates closely to that found for the association of bilateral epididymitis and bilateral seminal vesiculitis, which was 73·6% within the same interval of time.

Category (b). PATIENTS WITH UNILATERAL EPIDIDYMITIS ON ADMISSION, BUT WHO LATER DEVELOPED DISEASE OF THE OTHER EPIDIDYMIS.—There were 23 men who were admitted to hospital with unilateral epididymitis and later developed disease in the other epididymis (Table IX).

TABLE IX

Associated Genital Lesions in 23 Patients on Admission to Hospital

Genital Lesions.	RSV.	LSV.	BiSV.	RSV+RP.	BiSV+BP.	BP	RSV+BP.
Left epididymitis . .	...	2	1	...	9	1	1
Right epididymitis . .	1	...	...	1	7	...	...

Of the total there was palpable evidence of pre-existing bilateral pelvic disease in 19 (82·6%) before the onset of the second epididymitis.

Category (a). PATIENTS WITH PELVIC GENITAL DISEASE BEFORE EPIDIDYMITIS DEVELOPED.—While the whole investigation was being carried out I decided to examine rectally all the male patients in hospital suffering from tuberculosis other than tuberculous epididymitis. Well over 200 patients were examined on several occasions over a prolonged period, and in 30 men palpable abnormalities of the seminal vesicles or prostate were found. Observation of these 30 patients was continued for eighteen months, and in 12 instances epididymitis developed.

TABLE X

Pelvic Genital Lesions and Subsequent Localisation of Epididymal Lesions in 12 Men

Pre-existing Pelvic Genital Lesion.	Right.	Left.	Right and Left.
R.S.V.+R.P.	3	...	...
L.S.V.+L.P.	...	4	...
Bi.S.V.+B.P.	...	...	4
R.S.V.+B.P.	1	...	...

Table X demonstrates that in these men who had disease of the right seminal vesicle and right lateral prostatic lobe, the subsequent epididymal lesion was always right sided. Similarly, when the pelvic genitalia on the left side were involved the epididymitis occurred on the left side. The four patients who had bilateral pelvic lesions developed bilateral epididymitis, while the remaining man showed a right epididymitis after a previous rectal examination had detected disease of the right seminal vesicle and both lateral prostatic lobes.

SUMMARY OF PELVIC COINCIDENTAL LESIONS.—From the study of these cases I felt that the statistics definitely gave support to a clinical impression of which I had been more and more aware with each additional patient examined. The impression that, no matter how early the tuberculous epididymitis, a lesion of the pelvic genitalia could be felt per rectum in the great majority of patients, did not gain much support from the extensive literature on the subject. Most writers agree that superficial and pelvic genital lesions are invariably associated, but rarely is the duration of the epididymal lesion given and so it is difficult to assess their results.

Many writers mention the difficulty of diagnosis with regard to prostatitis and vesiculitis, and all agree that there is a certain percentage of error in any results. These writers also agree that the diagnosis of epididymitis, from whatever cause, is an easy one to make, but experience and a certain amount of skill are necessary to find a slightly enlarged or thickened prostate or seminal vesicle. In my opinion,

given average skill and considerable experience of rectal examinations, the percentage of error will tend to cause an under-estimation in the number of cases with prostatitis and vesiculitis rather than an over-estimation. I have been unable to find any reference in literature wherein the prostate and seminal vesicles had been found to be normal at operation or post-mortem examination when a previous clinical examination had detected apparent tuberculosis. On the other hand, Young,[2] after some radical operations for the removal of the seminal tract, found disease of the prostate and seminal vesicles when clinical examination before operation failed to detect any abnormality. Cunningham [11] found similar results after autopsies on patients who had had tuberculous epididymitis.

From my own investigation, one outstanding feature in patients admitted to hospital with genital tuberculosis was that in 82 (43·9%), the associated lesions were found within three months, and in 16 (8·6%) within one month of the onset of the epididymitis. The actual percentage figures taken separately are not an aid to any conclusions as the numbers depend on the interval between the onset of the disease and the patients' admission to hospital. What is worthy of note is that the associated lesions were present at an early date in these patients and, of 16 patients examined within one month of the onset of epididymitis, 7 had bilateral seminal vesiculitis and 8 had bilateral prostatitis, and, of 82 men within three months of the onset of the epididymal lesion, 44 had bilateral prostatitis and 42 bilateral vesiculitis. Remembering the views of several authorities who stated that prostatitis and vesiculitis were difficult to diagnose, I felt at this stage that my statistics so far did not support either the views of Barney or Young, but, considering the difficulties in diagnosis and with the number of patients showing early bilateral pelvic genital disease, I tended more to the view expressed by Young.

In the 23 patients admitted with unilateral epididymitis, but who later developed disease of the other side, the rectal examination on admission showed bilateral pelvic disease in 19 instances. Barney admits that he has been unable to settle the manner of invasion of the second epididymis and states, " unless one takes the view that infection of the second epididymis is blood-borne, the lymphatics appear to be the most probable bridge between the prostate and the epididymis."

The percentage figure of 82·6 of cases in this section showing bilateral involvement of the pelvic genitalia before the onset of tuberculosis of the remaining epididymis suggests that the pelvic genitalia have a considerable influence over disease of the epididymis, and if Barney admits that the second epididymitis may be due to a spread of the disease from the pelvic genitalia, it appears to me to be unusual to postulate one method of infection of the first epididymis and another method for infection of the second.

I lay great stress on the last section considered, comprising 12 patients who were found to have pelvic genital disease without

epididymitis. The fact that these patients developed epididymitis later would appear to suggest the pre-existence of vesicular or prostatic disease or probably a co-existence of both for a considerable period before the onset of clinical tuberculous epididymitis. In each case a right-sided pelvic lesion was followed by a right epididymitis, a left-sided lesion of the pelvic genitalia by a left epididymitis and a bilateral pelvic lesion by bilateral epididymitis. No case was found in which infection of an epididymis followed tuberculosis of the contra-lateral pelvic organs.

CONCLUSION.—While the numbers considered are small, the results appear disproportionately impressive and, taken into consideration with what has already been said concerning the relationship of epididymitis and disease of the deeper genitalia in the two large groups, lead scarcely to any other conclusion than that *vesiculitis or prostatitis, or both, precede the more peripheral genital lesion*. At the very least it has been established that prostatitis, vesiculitis and epididymitis constitute a clinical unity. It might further be hazarded that such a distribution of lesions presupposes a central common focus.

ASSOCIATED RENAL LESIONS

The rôle of the kidney in the pathogenesis of genital tuberculosis in the male has been the subject of discussion for many years. That renal and genital tuberculosis are frequently coincidental has been stated by many writers, but opinions differ greatly as to the exact relationship, if any, between the two. The fact that cystoscopy, intravenous and retrograde pyelography are procedures which are not devoid of risk to a tuberculous patient deters some from a complete renal investigation in cases of genital tuberculosis, while others believe that the risk to a patient is greater if these procedures are left undone in that a renal lesion may be overlooked. A third view is that tuberculous epididymitis is a certain sign of renal tuberculosis and demands a full investigation.

ANALYSIS AND DISCUSSION OF PRESENT DATA.—Among the 402 cases of tuberculous epididymitis, 140 (34·8%) were diagnosed as also suffering from renal tuberculosis. In addition, 50 others were labelled as probably suffering from renal tuberculosis and 51 as possible cases of renal tuberculosis.

A rectal examination was carried out in 114 of the 140 patients with definite renal disease with positive results in 110 (96·5%). Seventy-eight men were diagnosed as having renal tuberculosis before epididymitis. In the remaining 62, the genital lesion was diagnosed before a full renal investigation had been carried out and consequently before a diagnosis of renal tuberculosis was made. I could not determine which was the initial lesion, but, as renal tuberculosis may be well established before symptoms arise, I considered that in many the onset of the urinary symptoms followed so closely on the epididymitis

that the renal lesion probably preceded the genital one. Forty-four of the 62 men on admission to hospital were found to have symptoms referable to the urinary tract. Seventeen had no urological symptoms, but one patient was admitted after nephrectomy and orchidectomy had been carried out elsewhere. The 17 men without symptoms all suffered from tuberculous epididymitis at the time of admission, and routine examination revealed pyuria and tuberculous bacilluria. Complete renal investigation showed unilateral renal disease in 14 men and bilateral disease in 3. One patient had unilateral epididymitis and 16 bilateral epididymitis, the duration of the epididymal lesions varying from 11 cases within six months, 15 within one year to one within two years.

In the 101 cases of suspected renal disease, only 8 cystoscopic and 6 intravenous pyelographic examinations were carried out. On cystoscopy, 4 of the 8 patients were found to have cystitis and in one other patient infection of the bladder was seen in the region of a dilated ureteric orifice. The 6 intravenous pyelograms showed normal kidney shadows. From these findings it cannot be proved that these 101 patients were free from renal tuberculosis, but there is much to support the view that they had renal disease. All suffered from tuberculous epididymitis, and 84 (83·1%) had definite tuberculous lesions outwith the genito-urinary tract. Albuminuria was present in every patient and, in addition, 76 (75·5%) had pyuria, 45 (44·6%) had urological symptoms and 50 (49·5%) had a tuberculous bacilluria. If these 101 patients are considered as having renal tuberculosis the association of the two conditions occurred in 241 (60%). The remaining 161 patients of the total 402 did not undergo any renal investigation, since there was neither sign nor symptom to suggest the necessity for such investigation. It is to be remembered that these were the earlier cases in this series and under present standards such failure to investigate would be deemed negligent. In my opinion and from experience since this investigation started, the *men with epididymal tuberculosis in whom tubercle bacilli cannot be isolated from the kidney urine are extremely few in number.* Frequently, the bladder mucosa has appeared healthy, the urine has been free of albumen, yet guinea-pigs have been found to be tuberculous after inoculation with the urine from the kidneys of these patients. Pyelography has frequently shown normal kidney shadows in these men, but, accepting the results of Medlar,[12] Jacobs,[13] Mack[14] and Band,[15] sub-clinical tuberculous lesions of the kidneys may be diagnosed on bacteriological findings alone.

The exact relationship between the onset of renal and epididymal tuberculosis was next considered. From the 140 men with definite renal tuberculosis, 78 were known to have the renal lesion before the epididymal one. In the remaining 62 men, 17 had no urological symptoms yet renal disease was found, and the duration of the epididymitis in 16 of these men was under one year. Twelve of the

62 men had urological symptoms but were unable to state either the time of onset of these symptoms or when the genital lesion appeared, while in 2 men the diagnoses were made in another hospital. Of the remaining 31 cases, the onset of the urological symptoms and the appearance of the epididymal lesion were simultaneous in 5, symptoms preceded the genital lesion in 3 and followed in 23 cases. In the 101 patients with suspected renal disease, 45 had urological symptoms.

TABLE XI

Relationship between the Time of Onset of Urological Symptoms and Tuberculous Epididymitis in 185 Patients

No. of Cases with Urological Symptoms before Epididymitis.	No. of Cases with Urological Symptoms after Epididymitis.	Nol of Cases with Simultaneous Onset of Symptoms and Epididymitis.	No. of Cases in which Relationship Unknown.
106	31	13	35

Subtracting the 35 in which the times of onset were unknown, the total becomes 150. Urological symptoms preceded the epididymal lesion in 106 (70·7%) and, if the views of many authorities are accepted, the renal lesion almost certainly preceded the epididymal one in the 13 with simultaneous onset of symptoms and epididymitis. Thus, in 119 (79·3%) the renal lesion started before the epididymitis. In the remaining 31 cases it is impossible to state which lesion was the initial one, but in over 60% of the cases urological symptoms appeared within one year of the start of the epididymitis.

Rectal examinations were carried out in 114 of the 140 cases of proved renal tuberculosis with positive results in 110 (96·5%). In the 101 men with probable tuberculosis, 51 patients were examined rectally with positive results in 48 (94·1%). By addition rectal examination of 165 patients with renal tuberculosis revealed palpable abnormalities of the prostate and seminal vesicles in 158 (95·8%). The difficulties of palpating pelvic genital disease have been stressed, difficulties sufficient to account for 4·2% or 7 negative results out of 165 cases. At this stage I felt that I had established a clear relationship between tuberculous epididymitis, seminal vesiculitis, prostatitis and renal tuberculosis.

An attempt was made to investigate the present condition of all the available patients who were dismissed from hospital between 1921 and 1941. I made personal contact with some, but most of the limited success I owe to Dr S. Laidlaw and his Tuberculosis Officers. Each patient was asked to attend Robroyston Hospital for examination. When possible, and with the patient's consent, intravenous pyelography and sometimes cystoscopy were undertaken. In addition, each patient was asked to send a specimen of urine for guinea-pig inoculation. Since the records go as far back as 1921, it was not surprising that

to the exterior and may be driven by drops into the ejaculatory ducts and so to the vasa deferentia. The proof that the urine may pass upwards along the vas deferens has been observed in cases of urinary fistulæ following orchidectomy, the fistulæ being through the inguinal incision. I myself had one case in which there was an escape of urine deliberately coloured with methylene blue, from a fistula in the inguinal region after epididymectomy.

According to many authorities the lumen of the vas deferens is undoubtedly the route for septic infections. The epididymitis which occurs in patients with prostatic enlargement is usually rapid in onset, and it has been asserted by some that acute epididymitis may be prevented by vasectomy prior to a surgical prostatectomy. In septic cystitis, severe epididymitis may follow instrumentation, suggesting a mechanical factor rather than an exacerbation of an insidious focus such as you might expect in lymphatic spread.

Experimentally, Rolnick[17] found that he was unable to inject fluids through the vas deferens beyond the tail of the epididymis, and he concluded that bacteria from an infected vesicle travel along the lumen of the vas deferens but are prevented from passing upwards beyond the tail by the same mechanical or anatomical factors which prevented the forcing of fluids beyond the tail. Peristalsis of the vas deferens has been demonstrated, but reverse peristalsis is not generally accepted, although two workers claimed that it occurred after stimulation of the verumontanum. It has been found, however, that when fluid is injected into the vas deferens and the vas then stimulated, the fluid progresses backwards by gradual stages to the epididymis, following each peristaltic wave towards the posterior urethra. O'Connor[18] reported two patients with retention in whom the bladder was emptied and a silver solution inserted. The following morning vas ligation was carried out prior to cystoscopy and indwelling catheter insertion, and when the vas deferens was opened the silver solution was obtained. He concluded that when epididymitis occurred after the vasa have been ligated it is probably due to a pre-existing deposit of infected material in the tail of the epididymis and not to subsequent infection of the lymphatics.

I am convinced that my findings lend support to the view that the *spread of tuberculosis to the epididymis takes place in the majority of cases by the lumen of the vas deferens*. The incidence of tuberculous epididymitis is highest during the years of maximal sexual potency, when the vas deferens would be expected to be most active. Anatomically, the vas consists of a thick layer of unstriped muscle running in a longitudinal direction only with the mucosa arranged in longitudinal folds. With active peristalsis it is reasonable to suppose that actual shortening of the vas occurs, followed by relaxation with possible resultant suction towards the epididymis. It is also my belief that the great majority of patients with tuberculous epididymitis have or have had a tuberculous bacilluria from a clinical or subclinical lesion of

the kidney. In many cases the kidney lesion heals or becomes quiescent and urological symptoms may never occur. The urological symptoms manifest themselves at a late date in renal tuberculosis and many clinicians are prone to wait for these before suspecting renal tuberculosis. Within recent years it has been the practice in Robroyston Hospital to investigate fully all cases of tuberculous epididymitis with or without urological symptoms, and the percentage showing renal involvement as demonstrated by the isolation of tubercle bacilli from the kidney urine has been almost 100. Many of these patients have not shown a destructive lesion judged by pyelography and close observation has been instituted in these cases.

The tuberculous prostate or seminal vesicle appears to be the link between the kidney and the epididymis. With tubercle bacilli in the urine, the step is a short one to the posterior urethra and thence to the prostate and seminal vesicles. It is possible that heavy work or straining may force a little urine into the posterior urethra, and from there it may pass into the ejaculatory ducts and so to the vasa deferentia. In a patient with tuberculous cystitis it is easy to appreciate how an irritable bladder tends to force urine into the posterior urethra, often at a time inconvenient for micturition, and even if the patient resists the warning small amounts of urine with tubercle bacilli may lodge in the posterior urethra. Also, part of the mechanism of micturition takes place in the posterior urethra and again urine may lodge there. By these methods infection of the prostate and seminal vesicles probably occurs and the risk of extension to the epididymis by way of the vas is present. With involvement of the pelvic genitalia the corresponding lymphatic channels are probably next to be invaded, and the obvious chain of channels along the vas deferens may be palpably involved. When the epididymis becomes diseased, the lymphatic channels, particularly those draining the area of the globus minor, also become involved and clinically the channels which accompany the artery to the vas may be enlarged. In that way, the clinical picture described by some and noted by myself on twelve occasions of epididymitis associated with thickening of the lower and upper thirds of the vas deferens with the middle third free of obvious disease may be observed. Recently I had a case of vasitis, prostatitis and seminal vesiculitis without epididymitis. The histological examination showed occlusion of the vas deferens with tuberculosis of the surrounding tissues, a condition which would be noted clinically with ease if it were always a precursor of epididymitis.

Against the theory of blood spread is the fact that the lesion associated with mumps, where blood spread is accepted, is in the testis, and also no record exists in Robroyston Hospital where there was coincidental tuberculosis of the fallopian tube and the kidney. The frequency of bilateral involvement of the epididymis is in favour of a local spread since in surgical tuberculous lesions, where blood spread is accepted, it is an extreme rarity to have symmetrical involve-

ment. In the case of renal tuberculosis where blood-borne bilateral involvement is accepted, the bilaterality occurs at or about the same time. With the same blood supply to the testis and epididymis, and moreover, with a large branch of the spermatic artery passing to the globus major, it would indeed be strange if the primary genital lesion were usually situated in the globus minor.

Finally, after a series of 12 cases of vasectomy of the healthy vas deferens in patients with unilateral epididymitis, follow-up of some years has yet failed to show recurrence of the epididymal disease.

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SYMPOSIUM ON TUBERCULOSIS NURSING *

I. INTRODUCTION

By H. BAXTER, Bridge of Weir Sanatorium

IT is a pleasure to open this subject which, while somewhat outwith the Society's normal medical, surgical and scientific studies, is, nevertheless, in the light of present conditions, of vital importance to the whole future of our campaign against tuberculosis.

It is obvious to all of us who are associated particularly with the dispensaries and hospital side of tuberculosis work, that the price of victory in the recent war includes the chaotic condition which exists to-day in many hospitals and especially in sanatoria. This applies to a less extent to the dispensary service.

Many of you are doubtless aware of the closing down in the city and country of small hospitals or sanatoria or tuberculosis sections in infectious diseases hospitals. This action increases the already large number of patients on the waiting-list of local authorities and is indicative of the major problem of tuberculosis nursing, *i.e.* the present shortage of staff.

In Scotland alone the tuberculosis staff shortage has been rising steadily and at the present day, for about 5000 to 6000 beds, must lie between 500 and 750 nurses, and this quite exclusive of certain E.M.S. hospitals accommodating tuberculous patients and staffed principally by C.N.R. nurses.

CAUSES OF THE SHORTAGE OF NURSES.—Let us examine possible causes of this major problem, to which most other problems are subsidiary.

I am of the opinion that the *control of nurses by the Ministry of Labour* is the principal factor, and I cannot understand why this control should not be dispensed with immediately. The fact is that a considerable amount of damage has been done, and we must be prepared to pass through a very trying period before any evidence of improvement will become manifest. There are other factors which some of you no doubt will think of prime importance, for example *lack of domestic staff.*

The Department of Health is always a pretty target when hospital and nursing affairs go wrong, and while some criticism may be levelled at the Department, the smaller hospitals and sanatoria, I am sure, were grateful for the seconding of C.N.R. nurses, even although these nurses were administered in sub-minimal lethal doses ! The Department's outcry regarding skin testing and exclusion of negative re-actors from nursing may have been something of a necessary evil.

* A discussion held at a meeting of the Tuberculosis Society of Scotland, held in Edinburgh on 26th October 1945.

Much has been written and something obtained during the recent war by way of propaganda, but *propaganda* has been a complete failure in regard to the recruitment of nurses into tuberculosis service. Some recent articles and letters to editors have not helped, rather I may say, have put the minds of the public against such a career for their young daughters.

The Minister of Health has, however, recently decided that all Mantoux-negative nurses need not be excluded from training in tuberculosis wards, either in chest hospitals or in general hospitals.

RECRUITMENT AND TRAINING.—We will await with interest Miss Renton's talk of recruitment and training, and I hope that many of you will air your views on training of the ideal tuberculosis nurse. Is it necessary that she should be general trained and specially trained in tuberculosis ? There is the problem of the independent training school for the *Tuberculosis Association Certificate* and of *affiliation* of small sanatoria to training schools. The advance in chest surgery and post-operative nursing will require to be recognised. Is it necessary that the nurse should have special salary for the sanatorium post ? Does this not savour of a bonus for a dangerous occupation ?

Tuberculosis nursing was the subject of a recent report by the Committee of the Tuberculosis Association and Joint Tuberculosis Council. It stresses, particularly, specialised training for the nursing of tuberculous patients. The General Nursing Council recently has proposed rules governing the inclusion of specialist tuberculosis nurses in the State Register of Nurses. These are two important points for consideration.

The problem of recruitment is to-morrow's problem, as the Government still hold many nurses trained and partly trained who might serve as useful recruits, but there is no reason against discussion to-day.

THE HEALTH OF THE TUBERCULOSIS NURSE.—Perhaps much of the adverse attitude towards training in a tuberculosis hospital or sanatorium is due to the somewhat loosely worded articles and letters in the papers regarding the dangers of young girls working in tuberculosis institutions ! I feel certain that you will all agree with me when I say that the attitude of the administrative members of the nursing profession will require re-orientation and that conditions of service, training and recreation for nurses will require in some instances considerable amendment if the career is to become attractive. I have no doubt whatever that you will await with great interest Professor Cameron's talk on the health aspect of the tuberculosis nurses, and I feel that it would be most useful if subsequently, from individual experiences of those of you interested particularly in this matter, you would indicate personal views to the Society. The problem undoubtedly exists, the problem of selecting healthy nurses and maintaining that health during their training period. The solutions to these problems are not difficult in the light of modern knowledge.

There are no figures available of which one can make a reliable statement as to the incidence of tuberculosis amongst nurses in virtue of their particular training school, be it general hospital or sanatorium. In Scotland the number of nurses who have become casualties in the last five- and ten-year periods has been comparatively small both for sanatoria and general hospitals.

From correspondence with various medical superintendents and matrons, I have ascertained that many of the sanatoria have had an extraordinary clean bill of health for the last ten-year period. There is, of course, the fallacy of inadequate follow-up.

On the other hand, one or two tuberculosis hospitals show a somewhat alarming figure of casualties, which creates undoubtedly an acute problem demanding an immediate solution.

With regard to the general hospitals, many of whom carry large staffs, the incidence is small and approximates that of the sanatoria. The collected figures for sanatoria and small hospitals with tuberculosis accommodation showed 37 nursing casualties in the last five-year period and 43 in the last ten-year period. We must remember war conditions and the increase in bed accommodation and nursing auxiliaries in certain hospitals.

Collected casualty figures for general hospitals in Scotland was 36 nurses in the last five-year period and 46 in the last ten-year period.

I very much regret that, as these figures have been given to me in confidence, I am unable to publish them in detail; but I do feel that a young girl runs no more risk of contracting tuberculosis in a well-run hospital, where her health and happiness is the prime consideration of the hospital authorities, than she would run by living and working in any other community, be it factory or the Services, or the basement of a large warehouse.

Despite all this, members of our allied profession do become sometimes afflicted with tuberculosis. It is then most essential that everything should be done immediately to treat the sick nurse; and then there arises another problem—that of the nurse's future career, re-education and rehabilitation of the sick nurse.

I have said sufficient to introduce the subject matter, and have very much pleasure in handing over to Miss Renton.

II. RECRUITMENT AND TRAINING

By B. H. RENTON, Matron, Victoria Infirmary, Glasgow

RECRUITMENT.—I feel that the problem is a tremendous one, and hope I shall not prove a Job's comforter. The first aspect one must consider is shortage of recruits, and this has been influenced to some extent by the shortage felt in all hospitals during the war years.

Where do we find the field of training ? The patient suffering from tuberculosis is nursed in the fever hospital and the sanatorium, and at present in certain E.M.S. hospitals. Difficulties in recruitment arise for several reasons—predominantly fear, which is experienced by the young prospective nurse before she enters hospital, or during her first weeks there ; fear perhaps more on the part of her parents who have known of " a case " admitted to a sanatorium and considered, therefore, to be suffering from a fatal condition or one ending in invalidism. In my experience in Bangour Hospital I found that members of the nursing staff were quite willing to undertake tuberculosis nursing, and at the same time their parents refused permission in case they contracted the disease.

A second factor interfering with recruitment is the fact that the general hospital now accepts candidates for training at eighteen years— so that sanatoria no longer act as a possible avenue into the nursing profession at eighteen as they did when the gates of the general hospital were closed to those under twenty-one.

The geographical situation of sanatoria in the country is a deterrent in these days, when there are acute transport difficulties and the nurses feel the need of the life and entertainment offered in the cities.

Conditions of living in certain sanatoria are not good—a vicious circle is created by the fact of the present shortage which implies much harder work than would normally be required of the nurses.

Nurses who have suffered from the disease and are employed after recovery are looked upon with some doubt and anxiety by their colleagues. In this respect it is most desirable, almost an essential, that each should have a single bedroom—a plan which I found useful at Bangour.

Compensation.—The nurse should have reasonable security if she falls a victim. The recorded test cases make it very doubtful whether compensation is in the least adequate for those nurses who develop tuberculosis.

The Press has not sown the seeds of encouragement but of fear. It is invariably the sensational and unfavourable sides of tuberculosis work that are ventilated — commonly as a result of uninformed opinion.

TRAINING.—At the present time there are four main categories of training open to the tuberculosis nurse : (1) for a specified period in fever hospitals—to qualify for the General Nursing Council Fever Register ; (2) in certain sanatoria for the Tuberculosis Association Certificate ; (3) affiliated training—in a sanatorium for (*a*) one and a half years, (*b*) two years—followed by the same period in (*a*) fever, (*b*) general hospital, for Registration. In this scheme the candidate usually obtains the Tuberculosis Association Certificate before proceeding to her affiliated school, and may return later to the speciality ; (4) post-graduate training for one year, *i.e.* general trained nurse to obtain the Tuberculosis Association Certificate.

The qualities and qualifications desirable in the candidate may be summarised as follows :—

A fund of sound common-sense which the nurse can apply practically in carrying out her ward duties. (She is apt to seek abstruse reasons for certain common-sense regulations, *e.g.* those for her own protection.)

She should have a two to three years' secondary education or at least a reasonable educational standard.

There should be some arrangement by which she can attend a preliminary training school—either regional preliminary training school or locally in her own hospital (economically a hospital preliminary training school may be impossible)—and this should be followed by experience in the wards and clinical teaching. Later a " block " or " theory " period should be given to cover specialised tuberculosis nursing.

The Block System.—In this scheme the student nurse is not harassed with lectures during ward duty periods. Teaching should, in my opinion, include instruction on the convalescent case—his occupational therapy and rehabilitation.

Discipline is necessary and presents greater difficulty in any hospital dealing with long-term cases when there is a danger of the nurse losing the nurse/patient professional relationship and a relationship of familiarity developing, which has led in some cases to incidence of tuberculosis among the staff.

A higher ratio of trained staff is most desirable; if post-graduate training became the more popular type of training this would be achieved, but specific training in tuberculosis technique is essential. The general trained nurse is not alive to many important factors in the nursing of tuberculosis, especially in regard to infection. I have found that a few trained nurses coming for one year's training are good propaganda factors, and this can well result in an increase of recruits.

Finally, we must remind ourselves that up and down the country many trained nurses have done splendid work in sanatoria for many years and found it interesting and satisfying.

One last point I should like to mention again. A factor which I do believe influences the nurse when she considers working among patients suffering from tuberculosis—the nurse would like to be assured of financial security, in the event of her becoming a victim of the disease, during her illness, and the long period of convalescence and rehabilitation which will follow. This would allay the dread of becoming a financial burden to her parents, a definite deterrent to recruitment would be removed and more women, I hope, might then be willing to undertake this important branch of nursing.

III. THE HEALTH RISK IN TUBERCULOSIS NURSING

By CHARLES CAMERON, East Fortune Sanatorium

IN a discussion like this it is easy to present statements in a light favourable to one's wishes. I intend to make a purely factual statement, for we have a good deal of accurate knowledge which is based on facts.

INFECTION IN TUBERCULOSIS WARDS.—Nothing is gained by minimising the facilities for tuberculous infection which exist in a sanatorium. Geer (1932) wrote from the Ancker Hospital in St Paul's which has 975 beds, 215 of which are devoted to the treatment of tuberculosis. The nursing of these patients occupied four months of the nurses' three-year course, and he found that between the years 1920 and 1928, of 934 nurses employed in the hospital, 42 (4·5 per cent.) developed tuberculosis either during training or shortly afterwards. In 1928 Mantoux testing of all nurses was begun, and he found that of 94 nurses who were originally Mantoux-negative more than 90 per cent. reacted to tuberculin within a year of the commencement of training. He then found that of 219 nurses in other hospitals in St Paul's, not taking tuberculous patients, only 41·8 per cent. reacted positively, and the percentage remained practically constant among the nurses in each of the three years of training. In other words, these nurses were not acquiring tuberculous infection. In the last two years of the period of observation, of 110 probationer nurses who entered the Ancker Hospital for training six developed clinical tuberculosis, and of these six five were Mantoux-negative when they were enrolled. This represents a morbidity of 5·1 per cent.

Heimbeck's (1938) well-known figures are much worse. His material consisted of 1453 probationers entering the General Hospital, Oslo, which has a total of 2600 beds, 400 of which are devoted to the treatment of active pulmonary tuberculosis. The period of observation covered the years 1924 to 1936, and during those years 1453 girls entered for training. 54·7 per cent. were Pirquet-negative. The first point which emerged in his investigation was the rapidity with which the tuberculin reaction changed from negative to positive, the majority showing that change within two or three months, and all by the end of the three years' course of training. Comparing the corresponding age groups in the general population of Oslo, Heimbeck found that the change which took three years to effect in young nurses took twenty years in women of similar ages engaged on other work in Oslo. Put otherwise, the figure of infection, which for the control group of women was 5·6 per cent., was for nurses 41·3 per cent., and 34·3 per cent. of these developed tuberculous disease. Even among those nurses who were tuberculin-positive on enrolment the percentage of morbidity (1·2 per cent.) was double that of a similar group of women working in Oslo.

There is an extensive literature bearing on similar points, but I shall only quote from two more sources. The first is the Prophit

Trust Survey which was published in 1944. The Norwegian and American figures for tuberculin-negative nurses are high compared with those for this country. The Prophit Trust figures for this group is 19·8 per cent. among a total of 3764 nursing entrants to eleven large and several smaller hospitals. These hospitals were divided into two groups, one of which admitted cases of advanced tuberculosis, mostly to special wards, and the other of which did not admit tuberculous patients. The annual Mantoux conversion figures for these hospitals were far from complete, but those available showed a higher conversion rate in the first hospital group, where it reached 78·3 per cent. in one year as against 58·4 per cent. in the second group ; and they showed also in this first group a much more intense type of reaction than was found in the nurses who became tuberculin-positive in the second group. The morbidity among Mantoux-negative nurses was 7·3 per cent. as compared with 2 per cent. of the Mantoux-positive group ; but further discussion of that aspect, despite its extreme interest, is not apposite to the point which I wish to make.

The second paper to which I refer is an article by Edwards and Penman on primary tuberculous infection in a sanatorium staff. This paper deals with 242 healthy entrants to the staff of the Cheshire Joint Sanatorium during the years 1936 to 1943. One hundred and seventy were Mantoux-positive and 72 (30 per cent.) were Mantoux-negative. None of the first group developed tuberculosis. (In the Prophit Survey group there was a morbidity of 2 per cent. among Mantoux-positive staff.) Fifty of the 72 Mantoux-negative (70 per cent.) became Mantoux-positive, and 10 of these (14 per cent. of the total) developed primary or post-primary tuberculosis. This figure is higher than the Prophit Trust but lower than Heimbeck's figures. All of these people recovered completely with observation and treatment.

These statistics are confirmed by many others which I deliberately omit, and they bear out two points : (1) the danger of admitting Mantoux-negative staff to tuberculosis wards, and (2) the rapidity with which infection takes place in these wards. The first need not concern us, as the present policy is not to use such people in tuberculosis work. I shall only add to that that there are two sides to every question, and Edwards and Penman discuss another very interesting side of this one.

The second point requires a little consideration. The Prophit Survey gives a morbidity figure of 2 per cent. among nurses originally Mantoux-positive, and Heimbeck's figure of 1·2 per cent. was above the morbidity of a similar group of the female population of Oslo. The Prophit Report points out the difficulty of getting comparable figures relating to the general population, and it states that it is not possible at this stage to comment on the relative tuberculosis risk in nursing as an occupation. Their morbidity figure tallies closely with those drawn from twenty other sources which they quote. Remember that all deal with general hospitals and not with sanatoria.

THE INCIDENCE OF TUBERCULOSIS AMONG NURSES.—There are figures from various sources dealing with the prevalence of tuberculosis among nurses. Scheel in 1924 found a morbidity of 2·2 per cent. among 2913 nurses in Norwegian communal hospitals, and Ross found an incidence of 6 per cent. among 800 nurses trained during a four-years' period in twenty different hospitals, almost all of which were general, in Manitoba. Britton and Bollman give American figures of 2·2 per cent., Shipman and Davis give a figure, also American, of 2·6 per cent., and Geer, as already quoted, gave a figure of 4·5 per cent. The latter was in a hospital which admitted lung tuberculosis patients, and after the institution of precautions against infection that figure fell in a later survey to 1·6 per cent. There are other figures within these limits of 1·6 per cent. and 6 per cent. Most are between 2 per cent. and 3 per cent. This represents an apparently high incidence, but it deals with the young adult female group which has always a high incidence of tuberculosis, and it is difficult to draw comparisons. Heimbeck's analysis, however, showed that in Oslo at any rate nurses had higher tuberculosis morbidity figures than their sisters in other occupations. We can take this much as definite. The incidence of tuberculosis among nurses generally is not low.

THE INCIDENCE OF TUBERCULOSIS IN SANATORIUM STAFFS.— What then is the position of nurses in tuberculosis institutions? In the first place we must differentiate between the general hospital which has tuberculosis beds and the sanatorium which admits cases of tuberculosis only. Such figures as are available for the former indicate an incidence of disease which is above the average for the age group. Unfortunately there are few figures for the latter. There was published in 1926 a record of 996 nurses employed by the Welsh National Memorial Association showing an incidence of tuberculous disease of 1·1 per cent. Edwards found no instance of tuberculous disease among 170 of a staff (97 nursing, 68 domestic and 5 of other categories), all of whom were Mantoux-positive when they joined. There are no extensive, statistically exact, figures of any other kind to go on, for however careful one's records of staff may be, the unfortunate fact remains that sanatorium nurses are often birds of passage, and we lose touch with them after they go. Practically all superintendents of sanatoria, however, are agreed that tuberculous disease among their staffs is rare, and that has been my experience ; but there is no follow-up of those who have left. The perfect sanatorium does not exist and human nature is fallible and perverse. We know what should be done, but it is difficult to get it done. I do, however, think that enough is done in sanatoria to diminish the undoubted risk which exists for those who do not understand the disease ; and conditions of life in a well-ordered sanatorium are certainly conducive to good general health. That is evident in the healthy appearance of staff who have been in such an institution for some time.

Such vague statements, however, cannot discount the repeated infection which all tuberculosis workers undoubtedly receive, and

what the layman wants to know is the exact risk of disease which the work entails. Is the Mantoux reaction an index of immunity? There is no such thing as absolute immunity in tuberculosis, and this test indicates sensitivity and, by inference, partial immunity. It is no guarantee of permanent immunity, and the repeated reinfections to which nurses are exposed are an undoubted risk. Even those who support the theory of the bronchogenic origin of pulmonary tuberculosis from the primary focus or from a blood dissemination deposit acknowledge the risk of superinfections, particularly when frequently repeated; but until reliable sanatorium statistics are available we shall not know the exact significance of that risk. What we do know is that, as a practically universal experience, disease among initially Mantoux-positive workers in well-conducted sanatoria is extremely rare.

THE SPREAD OF INFECTION AND ITS CONTROL.—How is the infection spread? The droplet theory is well established nowadays, and fine droplets can float freely in the air. The heavy droplets have a short trajectory and land on bedding and floors, and the danger of dust infection is apparent—if the dust particle is sufficiently fine. The great source of dust is that necessary abomination, the hospital blanket, and the problem here is probably analogous to the problem of the spread of streptococcal infection. The solution may lie in oiling of blankets and floors. So far as the spread by droplets is concerned, the patient must help, and that is where the discipline of the ward and of the sanatorium counts. The handling of sputum containers is unpleasant. The risk is nil if the nurse wears overalls—which must always be worn in the wards—and gloves, or washes her hands immediately afterwards. Most infection then is inhaled and that suggests the idea of the mask, but the wearing of the mask here has a different purpose from the wearing of one in a surgical theatre or ward. There it is used to keep the droplet in. Here it is used to keep the droplet or particle out. The two are different, and unless a properly designed and standardised mask, which must fit as closely as a gas-mask, is used, the wearing of a mask becomes merely a perfunctory recognition of a danger. It is a soporific to people who do not understand, and it becomes itself a danger. The main preventive of infection will always be adequate ventilation of, and the free access of sunlight to, the wards.

There is still another. The nurse, like the soldier, marches on her stomach, and her conditions of life must be the best, and not what a spurious economy thinks she will put up with. Her work is often harassing and monotonous and her private life must be her own; for an emancipated spirit fortifies a well-tended body, and strength of body and serenity of mind are the best defences against tuberculous invasion.

SUMMARY.—1. The nursing of lung tuberculosis involves exposure to repeated infection.

2. That is dangerous to young Mantoux-negative adults. This point need not enter into the discussion.

3. There is theoretical danger to young Mantoux-positive adults,

but there are no complete sanatorium statistics bearing on this point. Such as there are, however, and the general experience of sanatorium superintendents, lead to the belief that tuberculosis in sanatorium nurses is less frequent than in the nursing profession generally.

4. The infection should be prevented at its source.   That means the training of patients and nurses.

5.. Tubercle bacilli die off quickly in wards exposed to direct sunlight, and even to full daylight.   Free ventilation dilutes floating infection and removes it from the ward.

6. Masks must be standardised and of approved efficiency for their purpose.

7. The question of oiling blankets and floors demands consideration.

8. The living and working conditions of tuberculosis nurses must be good.   Mental freedom is just as important as physical well-being.

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IV. REHABILITATION

By H. BAXTER, Bridge-of-Weir Sanatorium

I DO not propose to spend very much time on this subject, although I feel that if members of the nursing staffs should be unfortunate enough to become casualties with tuberculosis I must insist that we can never do sufficient to help them.   My experience of nurses as tuberculosis patients has been somewhat mixed—easy and difficult.   I have given much thought and consideration to the problem of post-sanatorium careers.   Unfortunately the instinct of the nurse is to carry on, and many a good nurse has carried on beyond the stage where a complete recovery can be obtained.   The nurse, like other patients, will therefore leave the sanatorium either completely stabilised, non-infectious and fit for work, or stabilised but infectious ; or non-stabilised with a rather guarded prognosis.

SURVEY OF 81 NURSES UNDERGOING SANATORIUM TREATMENT.— If there is time at my disposal I will show you a few figures from a

survey of 81 nurses treated during the last twenty years at Bridge of Weir Sanatorium. The figures are taken from the records and show that—

(1) Very few nurses are hospitalised under the age of twenty years, which does not bear out the assumption that many young girls fall victims to a heavy infection immediately they join as probationers. The bulk of these nurses were in the age groups 20-25 and 25-30 years. Group 30-35 show a marked fall in incidence, and after the " years of discretion " were reached very few nurses appear in the records.

(2) The Ministry of Health Classification applied to these 81 nurses show a non-infectious and closed lesion affecting 33 of the nurses, while 48 of them were positive sputum cases.

(3) The general condition of these girls on admission was " poor " or only " fairly good " in a large percentage of the cases, surely a somewhat grave reflection on the maternal instincts of our good matrons and on the paternal watchful eye of the superintendents or medical officers in charge of the nursing staffs. After treatment the condition of the nurses under review had improved to " good " or " very good " in 44 per cent. of the cases.

(4) Sputum was present on admission in 48 cases, and at the time of discharge 40 of the nurses, almost 50 per cent., still showed sputum. Our finding creates a difficult problem immediately we come to the rehabilitation of nurses, even although the sputum remains negative.

(5) Hæmoptysis was present in 31 cases prior to admission and in 14 cases during residence.

(6) Prior to admission pleurisy was present in 48 cases, and during residence in the sanatorium 24 of the nurses had an attack of pleurisy.

(7) During the period of residence 1 nurse died, 24 nurses were not weighed on account of their ill-health, 14 lost weight and in 42, or a little over 50 per cent., a gain in weight was exhibited.

(8) At the time of discharge it was estimated that 43 of the nurses were quite unfit for work, that 19 of the nurses were fit for light work and that 18 were fit for ordinary work, presumably to return to their nursing profession.

(9) I may add that in 25 of the cases a family history of tuberculosis was obtained and in 6 cases it was quite marked.

(10) For those interested in clinical findings, tuberculous laryngitis was present in 18 cases and intestinal tuberculosis in 4 cases.

(11) Various non-tuberculous complications were present calling for no special comment.

(12) An interesting fact was obvious in reviewing these 81 nurses, namely, that previous to admission to the sanatorium the place of employment was as follows : in general hospitals, 15 nurses ; in sanatoria and in tuberculosis wards, 32 nurses ; and miscellaneous, 3 nurses. It is regretted that in 31 of the records no information had been obtained.

(13) These girls were born : 46 in cities and 32 in the country and 3 in foreign countries. This finding rather upsets the well-worn theory

that the country girl going into the city shows immediately a flare-up of the tuberculosis contracted in the country districts.

(14) From the point of view of residence in the sanatorium for treatment, the figures indicate that the average nurse will require to stay a minimum of one year under treatment.

REHABILITATION.—Returning to the figures obtained for nurses leaving the sanatorium relevant to their fitness for work, one finds that about one out of every four nurses is deemed fit to return to her normal occupation ; but we must concern ourselves with the 25 per cent. of the nurses who are stabilised and fit for light work, but who may break down under the exacting life of a full-time nursing appointment. I feel strongly that some scheme subsidising the nurse for a period of twelve months after leaving the sanatorium is necessary. I suggest a scheme like that of compensation for silicosis, where the last employer receives the onus or responsibility. There is, of course, no scheme in Scotland like the Rehabilitation Nurses Scheme at Papworth, Godalming Sanatorium or Preston Hall, and I am certain that recruits to the nursing profession would be happier in the knowledge that some scheme existed which would completely safeguard their future health in the event of becoming afflicted with tuberculosis. It would not be sufficient to allow them continuous sick benefit, but it is essential to encourage them to live and work in spite of partial disablement. This I think is particularly essential in the case of the nurse who is non-infectious and who would be most suitable for re-employment in sanatoria and in tuberculosis hospitals.

The ideal appointment would be part-time, leading to full-time sanatorium posts, provided the sputum examination remains negative and the nurse under constant medical review.

Three barriers exist and are difficult problems—

(1) The barrier of superannuation by local authorities.

(2) The prejudice of matrons and superintendents against the employment of a tuberculous nurse.

(3) The attitude of other members of the nursing staff.

The existing scheme of the Ministry of Labour for the rehabilitation of disabled nurses (D.H.S. circular No. 81/1943) offered training to certificated nurses as : (a) industrial nurses ; (b) sister tutors ; (3) health visitors. This scheme, however, has proved a failure, as to date only one nurse, who had made a complete recovery from tuberculosis, has enrolled under this scheme. I feel certain that no greater stimulus can be given to recruitment than a complete scheme assuring the future of the nurses, but it is essential to commence rehabilitation in the sanatorium. It is necessary to carry out up-grading during convalescence and to re-establish confidence and self-esteem in the sick nurse at an early stage of such convalescence.

ACUTE INFLAMMATION AND ABSCESS FORMATION DUE TO A DIPHTHEROID BACILLUS

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IN October 1944 a diphtheroid bacillus was isolated which was studied because of the unusual clinical features of the case from which it was derived.   Human infections caused by proved pathogenic diphtheroid bacilli are sufficiently rare to warrant recording, although in this case the investigation could not be completed owing to the bacillus losing its virulence.

HISTORICAL

Infections caused by *Corynebacterium ovis* (Preisz-Nocard), *Corynebacteria pyogenes*, *renalis* and *equi*, and by *Listerella monocytogenes* will not be considered in this review as the organism was proved not to be any of these varieties.

Two groups of other pathogenic diphtheroids can be distinguished in the literature : those isolated from the human and those from the animal host.   The latter group will be summarised first.

Animal Infections.—The first to describe an infection of mice by diphtheroids was Kutscher[1] in 1894.   The causative organism produced nodules in the internal organs.   The mice succumbed after a few days, but guinea-pigs, rabbits, cats, dogs and fowls were not affected.

In 1901 two laboratory infections were recorded.   One, by Bongert,[2] whose strain was also very infective for mice and produced numerous small abscesses in various organs ; but his strain was Gram-negative on isolation and only old cultures exhibited Gram-positivity.   Rats, guinea-pigs, rabbits, pigeons, fowls and sheep were immune.   His organism produced a toxin which was lethal for mice.   Klein[3] in the same year reported the isolation of a Neisser-positive strain from rats, which was also pathogenic for guinea-pigs.   Injected subcutaneously only a local infection resulted.   The infection was not influenced in any way by 600 units of diphtheria antitoxin.

The strain of von Holzhausen[4] obtained from mice remained virulent for one year though cultured on artificial media.   The organism was pathogenic for mice only, guinea-pigs, rats, rabbits and dogs remaining unaffected.   Neither toxins nor local abscesses were produced, the mice dying of a septicæmia.

Human Infections.—One of the earliest recorded human infections due to a pathogenic diphtheroid bacillus is the case described by De Witt.[5]   His patient was a girl of sixteen who suffered from a

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generalised infection by a Gram-positive, Neisser-positive, but motile bacillus. This was pathogenic for guinea-pigs and also produced a toxin. The patient's blood agglutinated the organism up to a serum dilution of 1 : 50.

Parker,[6] in 1922, claimed to have isolated pathogenic diphtheroids frequently from the middle ear of cases suffering from otitis media, especially after scarlatina. His diphtheroids were Neisser-positive, required blood for their growth and caused a toxæmia in guinea-pigs, rabbits and mice. Diphtheria antitoxin (500 units) had no beneficial effect.

Gilbert and Stewart [7] recorded the isolation of a diphtheroid bacillus from the throat which caused necrosis in the guinea-pig after subcutaneous injection, and produced abscesses in liver and omentum after intraperitoneal injection. The organism produced a toxin which was only partially neutralised by diphtheria antitoxin. In a later paper [8] they suggested that the organism might be spread by infected milk.

Mair,[9] in 1928, published a note on a " strain of *B. diphtheriæ* showing unusual virulence for guinea-pigs," and his strain was included in the larger and very thorough study of Barratt [10] in 1933. Mrs Barratt was able to show that there are " aberrant " strains of *C. diphtheriæ* which will kill rats in 1-2 days after intraperitoneal injection and which are sometimes partly neutralised by the antitoxin of *C. diphtheriæ*, and sometimes by that of *C. ovis*. To quote her seventh conclusion : " Wherever the characters of the aberrant strain differ culturally or biologically from those of *C. diphtheriæ*, they approach, if not completely, those of *C. pseudotuberculosis ovis* (bacillus of Preisz-Nocard)."

The last paper relating to this subject which I was able to find was that of Barber, Guiseppi and Knott [11] in 1937, who record two cases, one of them previously published in 1920.[12] The first case was a subcutaneous infection by a diphtheroid bacillus which caused abscesses in the guinea-pig after subcutaneous injection, while another animal was protected against infection by diphtheria antitoxin. The organism was agglutinated both by the patient's and the guinea-pig's serum. The strain isolated from the second case caused necrosis after subcutaneous injection of the guinea-pig, but the animal could not be protected by diphtheria antitoxin.

INVESTIGATIONS ON THE ISOLATED BACILLUS

Patient's History.—The patient was a boy of 13 years, who was first seen by his doctor on 3.10.44. The latter found a pleural rub on the left side ; the temperature was raised to 101·4° F., with a pulse rate of 100 and respirations 30 per minute. The patient was put on a course of sulphathiazole. The temperature fell and the pulse and respiration became normal. He was allowed to get up. On

7.10.44 the doctor was called in again. He found the boy very distressed in his breathing, the temperature subnormal and there were no signs of air entry over the left lung. In this condition the patient was admitted to the Ear, Nose and Throat Department of the Royal Infirmary, Edinburgh. Here it was found that the inspiratory distress was due to a complete right-sided paralysis of the larynx. There was a large bulge coming from the right sub-epiglottic region with an intensely red surface, but *not* covered by a membrane. A tracheotomy was performed. During the operation the cause of the swelling, which was bulging into the trachea and partially blocking it, was found to be an abscess with free pus, situated between the lower border of the cricoid, trachea and posterior sheath of the thyroid. The patient made an uneventful recovery. No growth was obtained from the pus of the abscess, though the direct films showed clusters of Gram-positive filaments which appeared to show branching. But cultures from the larynx, taken through the tracheotomy opening from the highly inflamed mucous membrane yielded a growth of diphtheroid bacilli on four different occasions (the last on 23.10.44). The first culture was pure, those obtained later mixed with *Staphylococcus aureus*, and later still with hæmolytic and non-hæmolytic streptococci.

Source of Infection.—Immediately a search was instigated as to the source of the boy's infection. It appeared that some six weeks ago he and a friend had acquired two rabbits, the larger of which had died three weeks before his illness. His friend and the surviving rabbit were healthy and no similar bacillus could be obtained from the latter.

Description of Bacillus.—The organism was a short Gram-positive bacillus measuring $2 \times 0.3 \mu$. It was non-motile, not spore-bearing, with a tendency to club formation, especially in older cultures, and also to branching. In fluid cultures the organism assumed a coccoid form. With the Neisser-stain polar bodies could be demonstrated in about 30 per cent. The bacillus was not acid-fast. It was a facultative anaerobe and grew best at 37° C. on all ordinary media including the tellurite plate, on which the colonies were large, smooth and black. No growth, however, was obtained on MacConkey's medium. On agar and Löffler slopes an abundant growth was obtained, smooth, glistening, slightly cream coloured, not unlike a staphylococcal growth.

Gelatin and coagulated serum were not liquefied. No hæmolysin against human and sheep red blood corpuscles was produced on solid or in fluid media. Nitrates were not reduced and no formation of H_2S occurred. Indol was not produced and the phosphatase reaction was negative.[13] Litmus milk was not changed.

In Hiss' serum medium the organism fermented glucose, maltose, saccharose, lævulose, galactose and mannose with formation of acid only. Lactose was slightly fermented. No change occurred in

dextrin, starch, xylose, raffinose, inulin, mannite, salicin, dulcite and glycogen.

Its sensitivity to penicillin was about half of that of the Oxford *Staphylococcus aureus* strain.

The organism was readily emulsifiable and could be stored for a fortnight or longer at room temperature and in the refrigerator.

The principal characters of this bacillus are set forth in the Table and compared with those of the organisms of the same group.

Serology.—The patient's serum as well as the serum of the surviving rabbit failed to agglutinate the bacillus. Too much stress need not be laid on this as the infection was not a generalised one (*cf.* Hughes [14]). Twelve " normal " human sera, chosen at random, did not agglutinate the diphtheroid bacillus either.

Two rabbits were immunised by intravenous injections with live bacilli, and after six injections, given twice a week, their sera agglutinated the diphtheroid up to a serum dilution of 1 : 6400 at 37° C., and better at 56° C.

The following strains, obtained from the National Collection of Type Cultures, were not agglutinated by this serum. Three different strains of *C. ovis*, *C. flavidum* (No. 764), *C. murium* (No. 949), *C. murisepticum* (No. 807A), a diphtheroid strain type X (Daniels, No. 1929) and a *C. ovis* strain received from Dr Lovell. Of a great variety of diphtheroid bacilli, isolated from various sources, none was agglutinated by this serum. In addition, a Listerella strain, obtained from Professor Webb, was also not agglutinated.

Animal Susceptibility.—Rats, rabbits and cockerels, injected subcutaneously, intramuscularly, intraperitoneally, and/or intravenously with large numbers of live bacilli ($\frac{1}{2}$-5 slope cultures after 18-24 hours' incubation) proved to be refractory. It may be noted here that the blood picture in rabbits showed an increase in polymorphs, but no increase of mononuclears. Guinea-pigs were also immune, except for one animal which received the exceptionally large dose of 5 slope cultures intraperitoneally and died after 48 hours. No Straus reaction was observed. The post-mortem findings in this animal were those of a generalised purulent peritonitis and toxæmia. The organism was recovered in pure culture from the peritoneal fluid and the heart blood.

Otherwise mice proved the only susceptible animal, injection of $\frac{1}{2}$ slope culture proving invariably fatal within 24-48 hours after intraperitoneal or intramuscular injection. After subcutaneous injection the mice survived. The post-mortem findings were usually a purulent peritonitis after intraperitoneal injection, while twice after intraperitoneal as well as after intramuscular injection abscesses in the omentum were observed. Once a small liver abscess (3 mm. in diameter) was found, from which the organism was recovered in pure culture. The organism was recovered from the heart blood in all cases. No Straus reaction was obtained, and the adrenals never showed hæmorrhages.

Species	Growth on Ordinary Media	Type of Colony	Colour of Culture	Pathogenicity to Animals	Adrenal Hæmorrhages	Straus Reaction	Protection by Diphth.-antitoxin	Auto-agglutination	Production of Hæmolysins	Reduction of Nitrates	Liberation of H$_2$S	Indol Formation	Fermentation of Milk	Liquefaction of Gelatin & Serum	Neisser Stain	Production of Phosphatase	Glucose	Maltose	Saccharose	Dextrin	Starch	Glycogen	Lactose	Xylose	Raffinose	Inulin	Mannite	Salicin	Dulcite	Mannose	Lævulose	Galactose
C. diphtheriæ	+	Opaque discs, granular	Greyish-white	Guinea-pig, rabbits, birds	+	-	+	-	++	++	...	-	-	-	+	-	+	++	-	++	++	++	-	...	...	...	-	...	...	...	+	++
C. pyogenes	-	Minute, dew-drop like	Smoky-brown or bluish-white	Domestic animals; rabbits when injected intravenously	...	...	...	+	+	-	-	...	AC	+	-	+	+	+	++	+	...	-	+	++	-	-	-	-	...	+	+	+
C. ovis (Preisz-Nocard)	++	Small, thin, dry or large, friable	Greyish-white or creamy-orange	Guinea-pig, rats, rabbits	-	+	++	+	++	-	-	-	-	++	+	++	+	+	++	++	...	-	,	...	-	-	-	-	-	+	+	+
C. renalis	+	Moist, small raised	Greyish-white or cream	Cattle	...	...	...	+	-	-	-	...	AC	++	+	...	+	-	-	-	...	-	-	...	··	-	-	...	-	++	++	...
C. equi	+	Viscid, small	Red	Horse	...	...	...	+	-	+	-	...	...	-	...	...	-	-	-	-	-	-	-	-	-	...	-	-	-	-	-	-
Aberrant diphtheria bacilli (Barratt)	+	Small, thin or opaque, thick	Colourless, later cream	Guinea-pig, rats	++	...	++	...	-	...	-	...	...	+	+	...	+	+	-	+	+	...	-	...	-	-	-	...	-	...	...	+
C. ulcerans (Gilbert and Stewart)	+	As C. diphtheria	Colourless	Guinea-pig, rabbits	-	...	++	...	++	-	-	-	-	+	+	...	+	+	-	+	...	...	-	...	...	...	+	...	-	...	...	...
C. murium (Kuscher)	+	Small, round	Whitish-grey	Mice	...	...	...	...	...	++	-	-	A++	-	...	...	+	+	-	-	...	...	-	-	...	...	...	...	...	...	...	-
C. murisepticum (von Holzhausen)	+	Small, thin	Colourless	Mice	...	...	...	-	-	...	+	-	A	...	-	...	+	+	+	...	...	...	+	-	...	...	+	...	-	...	+	+
Listerella monocytogenes	+	Very small, dew-drop like	Transparent, later whitish	Rabbits, guinea-pigs, mice, sheep	...	...	...	-	++	+	...	-	A sl.	-	++	+	+	++	+	...	...	++	++	-	-	+	+	++	-	...	...	·-
C. flavidum	+	Wrinkled	Yellow	Laboratory animals	...	...	...	-	++	-	...	-	A sl.	-	...	-	+	+	++	...	-	...	...	...	...	...	...	...	...	...	...	...
Own strain	+	Round, moist, viscid	Cream	Mice, feebly for guinea-pig	-	-	...	-	-	-	...	-	-	-	+	-	+	+	+	-	-	-	+sl.	-	-	-	-	-	-	-	+	+

To illustrate the post-mortem findings the following histological reports are given :—

1. Two mice, injected intraperitoneally with $\frac{1}{2}$ slope culture. Death occurred within 48 hours. Both mice show essentially the same changes. The most definite finding is an exudate on the peritoneal surfaces of liver and spleen. This contains polymorphs and mononuclears, necrotic cells and very large numbers of bacteria ; little, if any fibrin. The bacteria are short, Gram-positive rods ; a few forms show bipolar granules when stained by modified Neisser method.

The liver parenchyma shows parenchymatous degeneration. A superficial strip of liver tissue over a small area in mouse II is necrotic. Gram-positive bacilli are found singly and in groups throughout the sections, some in von Kupffer's cells, some apparently lying free.

The spleens and lungs show only active congestion with a little hæmorrhage in the lung of mouse I, and some œdema in the lung of mouse II. A few Gram-positive bacilli were seen in both spleens, none in the lungs.

None of the sections shows abscesses or areas of focal necrosis.

2. Mouse, injected intraperitoneally, death within 48 hours. The spleen apart from perhaps slight congestion of the pulp, is normal. In particular no abscesses are present within its substance, but a fair number of such lesions are adherent to the outer aspect of its capsule.

The liver shows slight irregular congestion and slight cloudy swelling. No abscesses occur in its tissue, but two or three small suppurating lesions occur immediately to its capsule.

The abscesses on the surface of the spleen and liver contain large numbers of Gram-positive and Neisser positive bacilli.

3. Mouse, died two months after intraperitoneal injection with 1/15 slope culture.

Both specimens are portions of fibro-fatty tissue (omentum ?). Very extensive areas of necrosis are present in the two specimens with moderate round cell infiltration at the periphery of the necrotic material. Numerous Gram-positive and Neisser-positive, very pleomorphic bacilli are present.

Toxin Production.—When freshly isolated the bacillus produced a filterable toxin. After three weeks' growth in broth 1 c.c. of the filtrate injected intraperitoneally killed mice within 24 hours. No other animal proved to be affected, even after injection of 5 c.c. The mice could not be protected by 500 units of diphtheria antitoxin.

It was decided to execute similar experiments with *C. ovis* antitoxin. Unfortunately, by the time a virulent strain of *C. ovis* had been procured and a toxin and subsequently an antitoxin had been produced, the bacillus, subcultured on artificial media, appeared to have lost its virulence as well as its powers of toxin production. The original toxin, though kept in the refrigerator, had deteriorated also by that time.

DISCUSSION

Though the organism was not grown on culture from the pus of the patient's abscess—of which only one specimen was received—it was found to be present in large numbers in the highly inflamed

tracheal mucosa. The same phenomena of branching and cluster formation, as seen in the original pus, were observed in old cultures. It can, therefore, be assumed that this diphtheroid bacillus was the cause of the abscess formation. This opinion is strengthened by the fact that the organism, when injected into mice, caused the formation of small abscesses of varying sizes, though admittedly frequently only of microscopical dimensions. However, larger abscesses did occur.

Identification of this diphtheroid bacillus offered difficulties. It was not a diphtheria bacillus, as, besides other criteria, no protection was obtained by the administration of diphtheria antitoxin.

The possibility of its being a Listerella could be ruled out on the ground of a too luxuriant growth, non-pathogenicity for rabbits and absence of motility, and no production of monocytosis, while serological reactions were negative.

As the bacillus grew well on ordinary media the possibility of it being a *C. pyogenes* strain need not be considered.

It was equally not possible to regard it as a *C. ovis* strain, as it possessed little pathogenicity towards guinea-pigs and none towards other laboratory animals, produced no Straus reaction and, *in vitro*, showed no auto-agglutination, and other negative qualities.

The literature as regards *C. murium* (Kutscher) is scanty. The main objection against its being regarded as a murine strain is the fact that it proved pathogenic for the guinea-pig, though only in very large numbers.

In all probability, if the last objection is recognised, this diphtheroid bacillus represents an " aberrant " diphtheria strain ; for this suggestion, unfortunately, the last and most valid proof is missing— the protection by *C. ovis* antitoxin.

The bacillus has been added to the National Collection of Type Cultures and has been given the number 6965.

SUMMARY

A diphtheroid bacillus is described, isolated from the tracheal mucosa of a boy suffering from an extra-tracheal abscess formation, which proved to be virulent for mice, feebly virulent for guinea-pigs, and produced a toxin which was not neutralised by diphtheria antitoxin.

Though conclusive proof could not be brought forward, various properties indicate that the organism has to be regarded as belonging to, or being related to, the " aberrant " diphtheria bacilli.

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NOTE

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and Triple Qualification the Royal Faculty of Physicians and Surgeons of Glasgow Board have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG. :—James Buchanan Bale, Gordon Brill, John Eric Burdett, Ephraim Brodie Cowan, Richard Murray Dykes, Abdel Fattah Mohamed El-Nomani, Gerald Winston Farrington, Jack Lane Fine, Janet Haddow Allan Fleming, Allan Foreman, Hanna Mikhail Makar Girgis, William Henderson, Mary Patricia Hughes, Frederick John Gerald Kinsella, Albert Kobina Kuta-Dankwa, Murdina Macrae, Ewen MacSween, Almena Miriam Maragh, Titus Aruna Morton, Robert Armstrong Kirkwood Ross, Elijah De Sarnan Sar, John Samuel Pattison Wilson ; and the following graduate of a recognised foreign University was also admitted a Licentiate :—Lother Seewald, M.D. UNIV. BONN.

NEW BOOKS

The Treatment of Mental Disorders (Ancient and Modern). By RICHARD EAGER, O.B.E., M.D. Pp. 100, with 7 illustrations. London : H. K. Lewis. 1945.

This little book, by a former Medical Superintendent, commemorates the centenary of the Devon County Mental Hospital. A brief account of the history of the care of the mentally ill since classical times is followed by a description of the development of the Devon Mental Hospital, viewed mainly from the administrative angle. A book such as this, recounting the evolution of a large mental hospital, will always have a sentimental interest for a psychiatrist. Nevertheless, we think that Dr Eager could have made it more interesting and inspiring ; for example, he might have said more about the medical work of Dr J. C. Bucknill, the famous first Medical Superintendent of the Hospital.

Pathology of Labour, The Puerperium and the Newborn. By CHARLES O. MCCORMICK. Pp. xviii+399, with 191 illustrations. London : Henry Kimpton. 1944. Price 37s. 6d.

This book, the main part of which is about abnormal labour and its management, also deals with the pathology of the puerperium and the newborn infant ; it is written in a most attractive, breezy and easily assimilated style. The subject matter is not accumulated from other textbooks, but is the result of Dr McCormick's own extensive experience, being prepared principally from his lectures to students.

It is fully illustrated, the illustrations being a very important feature of the book, in so far as they illustrate the various treatments described most adequately. The treatments themselves are described shortly, but due emphasis is made of special points to be noted and the dangers are equally well denounced ; this is done by putting these facts in big black print or in italics.

Although it is an American production, its teaching in the main is very little different from what is taught in this country and it is good to see that the latest

British methods, which have often not been fully recognised in American literature, have been included and favourably commented upon. Instead of having the large customary list of references at the end of each chapter, there are a limited number of selected references, mostly modern, which are inserted throughout the text. The book is written in the second person, which increases the pointedness of the instruction. This textbook is out of the ordinary and can be definitely recommended not only to students and doctors, but also to the younger specialists, as they will gain experience as to how difficult subjects should be taught to their students.

Pre-Excitation : A Cardiac Abnormality. By RICHARD F. ÖHNELL. Pp. 167, with 30 figures. London : Henry Kimpton. 1944. (Printed in Stockholm.) Price 15s. net.

Starting from an analysis of cases such as originally described by Wolff, Parkinson and White, in which the electrocardiogram in some individuals subject to attacks of paroxysmal tachycardia shows inconstant bundle-branch block associated with a short P-R interval, the author has grouped as of similar causation various other abnormal electrocardiographic curves. For example, cases with a constant P-S interval but deformity of P-R segment due to an abnormally early rise in the initial ventricular deflection are included. All variations of this type are considered explicable on the hypothesis of a double excitation of the ventricles ; a normal excitation following the usual a-v path, and an additional and slightly earlier excitation. The possible origins for such an additional excitation are fully discussed, and the evidence for additional auriculo-ventricular connections (Kent's bundle, etc.) are collected. Certain histological observations by the author on such additional muscular a-v bridges in some of his cases are presented, with good microphotographs. There are references to over 220 papers on curves of these types.

Despite the labour that has been expended in its compilation, and the excellence of format and reproductions, the book lacks clarity, and makes difficult reading even for the specialist. It should have a limited appeal to those interested in this special aspect of cardiology.

Malaria. Its Diagnosis, Treatment and Prophylaxis. By WILLIAM N. BISPHAM, M.D. Pp. vii+197, 5 plates. London : Baillière, Tindall & Cox. 1945. Price 19s. 6d.

The purpose of this book, as stated in the preface, is to give the physician a knowledge of the clinical features of malaria. The author has, however, included all aspects of the disease, the history from remote times, the geographical distribution, ætiology with a detailed description of the parasites supported by coloured plates, and some description of mosquitoes and their habits. Full accounts of modern methods of treatment are given. The book is well documented and at the end of each chapter a list of authorities is given in support of the writer's observations.

Psychology in General Practice. Edited by ALAN MONCRIEFF, M.D., F.R.C.P. Pp. 199. London : Eyre & Spottiswoode. 1945. Price 12s. 6d. net.

This book consists of seventeen sections by fifteen well-known writers. Twelve of the sections are revisions of a series from *The Practitioner ;* several of the other sections have been specially written for this volume. Each section is necessarily rather brief but the authors have been able to give much valuable information. This is not intended to be a systematic account of psychiatry ; it is a symposium on the aspects of practical importance to the general practitioner. The subjects are well chosen and touch upon many of the psychiatric problems of general practice. There is a valuable and comprehensive chapter on differential diagnosis by R. D. Gillespie ; and Rogerson gives an important account of the mild depressive psychoses Also included are chapters on psychiatric social work by a psychiatric

social worker and on sex problems by Griffith. There is a most practical chapter by Tattersall on the legal procedure for mental hospital admission and discharge— but unfortunately the Scottish procedure is not included.

Radium Therapy : Its Physical Aspects. By C. W. WILSON, PH.D., F.INST.P. Pp. xi+224, with 97 illustrations. London: Chapman & Hall Ltd. 1945. Price 18s. net.

The author has succeeded in his attempt to produce a book which will make the work of the physicist in radium therapy appear a more co-ordinate whole than hitherto. The treatment is not exhaustive but it is everywhere adequate and the bibliography at the end of each chapter makes it a simple matter to follow up any point in which the reader is specially interested.

Non-physicists should find the book fairly readable. Perhaps Chapters II and III—the interaction of high voltage radiation and matter, and the methods and theory of gamma-ray dosimetry—will present the greatest difficulty for such readers. The chapters on surface applicators and cavitary and interstitial radium therapy, containing as they do a full account of the Paterson and Parker system of dosage, are exceptionally useful. In the chapter on radium teletherapy the author rightly stresses the importance of thinking in three dimensions when considering dosage distribution. On the question of protection and total energy absorption, the author suggests the possibility that the accepted tolerance dose for gamma rays may be too high. The diagrams are all admirably clear though some of the plates could be improved.

By presenting the information in this form the author has made a valuable contribution and the book will be extremely useful to all workers in this field.

Annals of the University of Otago Medical School, 1875-1939. By D. W. CARMALT JONES. Pp. 286, with 12 illustrations. New Zealand: A. H. & A. W. Reed, Wellington. 1945.

This book has of course particular appeal to the Staff and Graduates of the Otago Medical School; but it has also a wider interest, for it is a record of the inception of a courageous adventure, a struggle against great difficulties and a culminating success, all in the comparatively short period of sixty-four years and within the jurisdiction of only three Deans. The first of these was a Scotsman, Dr John Scott, a pupil of Sir William Turner's, who went out as professor of anatomy from 1877 till his death in 1914. His successor, Sir Lindo Ferguson, retired in 1937, and to his vision, energy and practical enthusiasm the School owes its present high professional standing, its excellent modern buildings and equipment. To him the *Annals* are dedicated and their publication has been made possible by a grant from the Ferguson Fund.

Otago University and Dunedin, wherein it is situated, have many associations with Edinburgh and Scotland. Otago was a Scottish settlement and the street plan of Dunedin was named after that of Edinburgh. With true Scottish zeal for education the original charter provided for churches, schools and a university, and endowments for these were provided. The University was founded in 1869 with powers to grant degrees in Arts, Medicine, Law and Music. Only the perseverance of the early enthusiasts could have survived the apparently hopeless difficulties of founding a medical school out of practically nothing. But from their vision has grown a reality. From one student in 1877, who could only get preliminary instruction at Otago, the school has swelled to an average of over 300 from 1920 onwards who now can get a medical training as good as any in the world.

The author is a former professor of medicine at Otago University and, though these *Annals* of necessity require the recording of much factual detail, he is to be congratulated on producing a scholarly and interesting record of medical achievement.

The Medical Annual. Edited by Sir HENRY TIDY and A. RENDLE SHORT. Pp. 410, with 61 figures and 107 plates. Bristol : John Wright & Sons Ltd. 1945. Price 25s. net.

Another war-time issue of this well-known year-book represents a valiant effort to keep abreast of modern progress in every field of medical endeavour. Current literature has been searched and abstracted by a team of over forty specialists and the result is a comprehensive account of recent advances. Especially valuable at the present time is a review of the latest information on the use of penicillin.

The Medical Annual is a book which should be in the hands of every practitioner.

NEW EDITIONS

Handbook of Practical Bacteriology. By T. J. MACKIE and J. E. McCARTNEY. Seventh Edition. Pp. viii+720. Edinburgh : E. & S. Livingstone Ltd. 1945. Price 17s. 6d. net.

Most of the new material in the latest edition of this widely used handbook is to be found in the appendix, which numbers 42 pages. It includes recent information on the sulphonamides and penicillin. on fluorescent microscopy and the electron microscope, and on present methods of examining war wounds for anaerobic organisms.

In the first 22 chapters only minor alterations and additions have been incorporated, and it has been found possible to keep the first 564 page numbers identical with those of the sixth edition. There is new material on the filterable viruses and on bacteriophage.

This is an indispensable laboratory guide for bacteriologist and technician ; it is now enlarged beyond the scope of a manual for students.

Handbook of Diagnosis and Treatment of Venereal Diseases. By A. E. W. McLACHLAN. Second Edition. Pp. 370, with 160 illustrations, 20 in colour. Edinburgh : E. & S. Livingstone. 1945. Price 15s. net.

The appearance of a second edition in less than eighteen months indicates that this manual has had a favourable reception and has helped to meet the need for a concise presentation of this specialty. The therapeutic aspect especially is changing so rapidly that constant reviewing of the subject-matter becomes incumbent on authors. The introduction of penicillin alone has produced an upheaval and supplanting of traditional methods in the therapy of venereal diseases, and this new edition has endeavoured to cope with the very fluid situation.

In a small textbook like this, the selection of what to put in and what to leave out, of what to expand and what to contract, must be difficult, and opinions will differ as to what is, and what is not, suitable pabulum for the burdened minds of medical students. To compress a large subject into small and yet digestible bulk, to avoid over-elaboration and yet be sufficiently comprehensive—these are the problems to which Dr McLachlan seeks to provide a reasonable solution, and the popularity of his book with student readers will be a measure of his success.

The Tissues of the Body. By W. E. LE GROS CLARK. Second Edition. Pp. xi+388, with 120 illustrations. Oxford University Press : Humphrey Milford. 1945. Price 21s. net.

The second edition of this remarkably successful book includes reference to material which has been published during the war years.

The main trend of the work is to present an account of body structure and function

which breaks away from the conventional limitations of traditional anatomy; examples and experimental evidence are collected from very wide fields in histology, physiology, embryology and practical medicine and surgery. From this point of view there can be no one who can fail to enjoy and profit by the author's approach, and the style is most attractive and readable.

The practice of placing references to reviews and literature at the foot of the appropriate text-page is a most stimulating one, and there is no other source which gives introduction to such wide fields in biology, academic and applied.

The book can be highly recommended to anyone who wishes to appreciate anatomy and physiology as conjoint active partners in basic scientific and medical advancement.

The Rheumatic Diseases. Second Edition. By G. D. KERSLEY, M.A., M.D., F.R.C.P. Pp. xii+120, with 18 illustrations. London : William Heinemann. Price 15s. net.

This book contains a well-balanced and concise account of the etiology, pathology and treatment of rheumatic diseases. Much has been re-written, particularly in the section on treatment, where an admirable description is given of the latest methods and their rationale. A discussion of chronic infective arthritis and allied conditions is also now included. The book is well illustrated with photographs and skiagrams, but it is unfortunate that the text contains so many misprints. It should, however, continue to be a useful handbook on the rheumatic diseases.

Internal Medicine. Its Theory and Practice. In Contributions by American Authors. Fourth Edition. 1945. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P. Pp. 1575, with 70 illustrations. London : Henry Kimpton, 26 Bloomsbury Way, W.C.1 Price 50s.

The contributors to this textbook of medicine are not only eminent physicians but also teachers of experience, and in consequence the subject matter is clearly presented; the views expressed are well balanced, speculative hypotheses being noticeable by their absence, yet very recent advances in medical knowledge are included. British readers not acquainted with American literature may find some of the terminology strange, and certain standards such as a normal hæmoglobin of 15·6 grammes per cent. may appear unusual; but these are very minor points in an excellent textbook in which clinical acumen is given its rightful importance and laboratory findings placed in true perspective. An attractive feature in the book is the short history which precedes the description of the diseases, and a useful feature is the bibliography at the end of each section.

Irish Medical Directory and Hospital Year-Book 1945. Eighth Edition. Pp. 293. Dublin : Parkside Press Ltd. 1945. Price 10s. 6d.

This volume gives a wealth of information about medical affairs in Eire. In addition to an alphabetical list of qualified medical men, there are details of the various medical bodies and hospitals throughout the country.

Some fifty-odd pages are devoted to a series of excellent articles on various subjects of medical interest.

Introduction to Diseases of the Chest. By JAMES MAXWELL, M.D., F.R.C.P. Second Edition. Pp. xi+292, with 66 illustrations. London : Hodder & Stoughton. 1945. Price 12s. 6d. net.

Many additions and alterations to the text have been made to keep this book up to date. The present edition deals fully with the symptomatology of respiratory disease and with the physical examination of the chest. The radiological appearances of respiratory lesions are discussed at length.

The book is clearly and concisely written and can be thoroughly recommended to both student and practitioner.

Index of Differential Diagnosis of Main Symptoms. Edited by HERBERT FRENCH, assisted by H. DONTHWAITE. Sixth Edition. Pp. viii+1128, with 198 illustrations, many in colour. Bristol: John Wright & Sons Ltd. 1945. Price 84s.

First appearing in 1912, this book has been frequently reprinted and revised. It is a companion volume to the *Index of Treatment* issued by the same publishers. The editor, who has written many of the articles himself, has been fortunate in securing the assistance of eighteen leading specialists and the result is a veritable mine of information on many subjects. The articles are excellently written and extremely helpful. Considering the war-time scarcity of materials and labour, the book is a wonderful production. The illustrations have been carefully selected and are of a very high standard. The volume is one which any medical man would be proud to own.

BOOKS RECEIVED

AITKEN, ROBERT, M.D., F.R.C.P.E., F.R.S.E. The Problem of Lupus Vulgaris.
(*E. & S. Livingstone Ltd., Edinburgh*) 15s. net.

BAILEY, HAMILTON, F.R.C.S., F.I.C.S., and W. J. BISHOP, F.L.A. Notable Names in Medicine and Surgery. (*H. K. Lewis & Co. Ltd., London*) 15s. net.

CHAMBERLAIN, E. NOBLE, M.D., M.SC., F.R.C.P. A B C of Medical Treatment.
(*Oxford University Press, London*) (*Mr Geoffrey Cumberlege*) 10s. 6d. net.

COPE, ZACHARY, B.A., M.D., M.S., F.R.C.S. The Early Diagnosis of the Acute
Abdomen. Ninth Edition.
(*Oxford University Press, London*) (*Mr Geoffrey Cumberlege*) 12s. 6d. net.

COWAN, ALFRED, M.D. Refraction of the Eye. Second Edition, Thoroughly
Revised. . . . . . (*Henry Kimpton, London*) 24s. net.

CRAIG, CHARLES FRANKLIN, M.D., M.A., F.A.C.S., F.A.C.P., D.S.M., and FAUST,
ERNEST CARROLL, M.A., PH.D. Clinical Parasitology. Fourth Edition,
Thoroughly Revised. . . . . (*Henry Kimpton, London*) 50s. net.

EVE, FRANK C., M.D., F.R.C.P. Artificial Respiration Explained.
(*E. & S. Livingstone Ltd., Edinburgh*) 3s. net.

FRAZER, W. M., O.B.E., M.D., CH.B. M.SC., D.P.H., and C. O. STALLYBRASS,
M.D. (State Medicine), CH.B., D.P.H., M.R.C.S., L.R.C.P. Text-Book of
Public Health (Formerly Hope and Stallybrass). Eleventh Edition,
Revised and Enlarged. . (*E. & S. Livingstone Ltd., Edinburgh*) 25s. net.

GRINKLER, ROY R., Lt.-Col., M.C., and JOHN P. SPIEGEL, Major, M.C. Men
Under Stress. . . . . (*J. & A. Churchill Ltd., London*) 25s. net.

HARRIS, I., M.D. Studies in Hypertony and the Prevention of Disease.
(*John Wright & Sons Ltd., Bristol*) 12s. 6d. net.

HOBER, RUDOLPH. Physical Chemistry of Cells and Tissues.
(*J. & A. Churchill Ltd., London*) 42s. net.

KARNOSH, LOUIS J., B.S., SC.D., M.D., with the Collaboration of EDWARD M.
ZUCKER, A.B., M.D. A Handbook of Psychiatry.
(*Henry Kimpton, London*) 25s. net.

LAWRENCE, J. STEWART, M.D., F.R.C.P. The Sulphonamides in Theory and
Practice . . . . . (*H. K. Lewis & Co. Ltd., London*) 9s. net.

McCULLOCH, ERNEST C., M.A., D.V.M., PH.D. Disinfection and Sterilization.
Second Edition, Thoroughly Revised. . . (*Henry Kimpton, London*) 33s. net.

SADLER, WILLIAM S., M.D., F.A.P.A. Modern Psychiatry.
(*Henry Kimpton, London*) 50s. net.

SEABORN, EDWIN, M.D., F.A.C.S., LL.D. The March of Medicine in Western
Ontario. . (*The Ryerson Press, Toronto.*) (*Hatchards Ltd., London*) 30s. net.

STONE, EMERSON L., M.D. The New-born Infant. A Manual of Obstetrical
Peniatrics. Third Edition, Thoroughly Revised.
(*Henry Kimpton, London*) 16s. 6d. net.

TITUS, PAUL, M.D. The Management of Obstetric Difficulties. Third
Edition. . . . . . . (*Henry Kimpton, London*) 50s. net.

MANAGEMENT IN PROSTATIC SURGERY WITH SPECIAL REFERENCE TO OPERATIVE RISK*

By R. LESLIE STEWART, F.R.C.S.ED.

MORE than thirty years have now elapsed since the operation of suprapubic enucleation of the enlarged prostate became popularised in this country, largely due to Freyer's pioneer work. To start with it was usually carried out as a one-stage procedure, perhaps as a last resort in the presence of gross infection and retention, and was accordingly attended by a high mortality rate. Since these early days numerous modifications in management and operative technique have been introduced in order to lessen the inevitable risks of radical treatment and to obtain lasting relief of urinary obstruction caused by the various forms of prostatic anomaly. Milestones in this process of evolution, such as the adoption of the " two-stage " operation combined with gradual decompression of the grossly distended bladder, the efficient control of sepsis, and measures taken to promote a sufficient diuresis together with a proper fluid balance in the blood and tissues, are generally recognised as safeguards of prime importance, especially when dealing with the more advanced type of case in which the risks of renal failure are very real. Alterations in operative technique, some of quite sweeping character, have also been advocated. Of recent years the most outstanding has been the adoption of trans-urethral resection for certain forms of prostatic lesion, though for the ordinary type of hyperplasia with considerable enlargement of the gland, suprapubic prostatectomy still holds the field in this country.

Despite the many changes in management and treatment, it must be admitted that a survey of any considerable series of truly unselected cases of benign prostatic obstruction may show a mortality rate ranging up to 20 per cent. or more; especially in hospital practice. Admittedly this is a high figure for any pathologically simple condition, though certain factors militate against any drastic reduction. Probably the most important of these factors is to be found in the high incidence of some degree of urinary dysfunction in men of advancing years; so common is it that the usual night frequency and other associated

symptoms are apt to be looked 'upon as merely the price to pay for longevity. Gradually and insidiously, therefore, this dysfunction may progress to a state bordering on an overflow incontinence without particular notice being taken of it. The patient may remain for long apparently well, or there may be an insidious deterioration of health and mental vigour with signs of upset or disease in the gastro-intestinal, cardio-vascular, and respiratory symptoms. The danger is that any one of these subsidiary manifestations may be so predominant that it is regarded as the primary condition and its relationship to an under-lying prostatic obstruction may fail to be recognised. The patient who develops an acute retention relatively early in the course of his malady may thus be deemed fortunate, provided the implications of such a complication are appreciated and not forgotten should active micturition be re-established. Whatever the cause, there is no doubt that the majority of prostatics come under treatment in hospital at a relatively late stage of the disease when the effects of back pressure have reached such a pitch that only a carefully planned two-stage operative technique is possible. Some indeed have progressed beyond this, the renal damage being so great as to be irreversible.

A study of the hospital records of some four hundred prostatic patients has emphasised the fact that during these years of war the average prostatic case has come under treatment at a later stage than formerly. In such patients our primary object is concerned with the restoration of efficient renal function as far as that is possible, and in order to do so we must necessarily keep in mind those principles of renal physiology which are relevant to the problem of urinary obstruction and back pressure. My theme being the management more especially of the late prostatic case, it would seem appropriate to refer to these physiological principles before proceeding to an analysis of such a series and the deductions that can be drawn from it.

FUNCTIONS OF THE KIDNEY

The healthy kidney requires an adequate blood supply and an unobstructed excretory channel. Normally it works well below its maximum capacity and there is thus a considerable reserve of function-ing units to call upon when necessary. It excretes the waste products of nitrogenous metabolism, particularly urea and uric acid, also inorganic substances which are in excess of the optimum requirements of the body. It regulates the osmotic pressure relations in the blood and tissues, it largely controls the volume of the circulating blood, and regulates the alkali reserve by the excretion of basic and non-volatile acid radicles as required. All these actions are under the most delicate control, any minute change in the composition of the blood provoking an immediate response.

THE EXCRETION OF URINE

Each excretory unit consists of (1) a Malpighian corpuscle made up of the glomerulus and Bowman's capsule, (2) the first convoluted tubule, (3) the descending and ascending loops of Henle, (4) the second convoluted tubule, (5) the collecting tubule which opens into a duct of Bellini—the latter opening at the apex of the pyramid.

Through the glomeruli is filtered a fluid which is almost identical in composition with the plasma except for the absence of protein. The pressure in the glomeruli is high, but filtration is opposed by the osmotic pressure of the plasma proteins which amounts to 30-40 mm. of mercury. It follows that if the blood pressure is lowered, for example by post-operative shock, to such an extent that the glomerular pressure is reduced to 30-40 mm. of mercury, the excretion of urine must stop. Similarly, if there is such a degree of urinary obstruction that the hydrostatic pressure in the ureters approximates to the net glomerular filtration pressure, the excretion of urine must be greatly impeded or even cease.

In the normal kidney the glomerular filtrate is greatly modified as it passes down the tubules. According to Cushny's theory there is an enormous filtration through the glomeruli—up to 100 litres in 24 hours, but from this filtrate 98·5 per cent. of water is reabsorbed into the blood by the tubular epithelium and there is also a differential absorption of the various substances filtered, in proportion to whether or not they are required for the body economy. At one end of the scale are the so-called threshold bodies such as sugar, sodium and chloride, which are completely or partially reabsorbed. At the other end are the non-threshold bodies such as urea and sulphate which, being waste products, are almost entirely excreted and must therefore be enormously concentrated as compared with their values in the blood. That the function of the tubular epithelium is a physiologically active one is indicated by the fact that the osmotic pressure of the urine is considerably greater than that of the blood, while the high degree of oxygen consumption of the kidney is also significant. Further, there is evidence to show that the tubular epithelium probably actively excretes urea and sulphates, also that it may synthesise and secrete ammonia and hippuric acid.

It is clear that this whole delicately co-ordinated mechanism of renal function and excretion must inevitably suffer when subjected to the continued effects of back pressure from prostatic obstruction. Once the hydrostatic pressure is raised to a sufficient degree, the kidney must reduce the concentration of the solids it excretes in the tubules in order to go on functioning. For a time there will be few demonstrable evidences of damage while the available renal reserve is mobilised, but sooner or later there will be forthcoming proof of impaired function as shown by a lowering of the concentrating power, and as the renal reserve is used up, so will the urea content of the

blood start to rise. It cannot be too strongly stressed that while a raised blood urea reading definitely indicates impaired function, the converse does not hold good. In other words, a patient whose renal reserve is almost entirely exhausted may still show a comparatively normal blood urea reading. Similarly a fall in the reading almost to normal after a period of preliminary drainage of the bladder does not in itself constitute proof that the patient is fit and ready for a prostatectomy. In assessing any given case it is important to consider the possibility of structural changes caused by a preceding chronic nephritis, while it is obvious that the presence of active infection will gravely complicate the issue.

Before leaving the subject of applied physiology, reference should be made to the mechanism of renal failure following upon too rapid decompression of the chronically distended bladder. In such cases the sudden release of hydrostatic pressure within the tubules may induce an acute venous engorgement which slows the blood flow to a dangerous level and results in asphyxial damage to the glomerular epithelium. Blood cells and albumin are then allowed to permeate into the lumen of the tubules and, in severe cases, there may be actual arrest of urinary secretion. In favourable cases the progress of this process may be arrested by reproducing the *status quo ante*. The hydrostatic pressure is again raised by filling the bladder, and an isotonic solution of a non-threshold body, namely sodium sulphate, may require to be administered intravenously with the hope of producing a diuresis sufficient to wash through the tubules which have become blocked by masses of red cells.

CLINICAL REVIEW

Generalisations based on relatively few clinical observations are often misleading, and I am therefore most grateful to Sir Henry Wade for his permission to include in this review all the prostatic cases admitted to his charge in the Royal Infirmary during the period in which I acted as his assistant surgeon. Personal cases treated in the Infirmary and in a smaller provincial hospital since 1940 are also included to furnish a total of some four hundred cases. As only certain aspects of the problem of management are to be considered, it will simplify matters if attention is confined to the commonest type of pathological change, namely the hypertrophied or adenomatous gland.

Incidence.—Though apparently numerous, the actual numbers of prostatic cases in a general surgical charge, even in one specially concerned with urological work, is not so large as might be expected. During a period of nearly eight years in Mr Wade's charge, they accounted for only 3·6 per cent. of the total admissions.

Pathological Classification.—Table I shows the total number of cases and the percentages of the three main types of disease. The

number of patients with chronic interstitial prostatitis or fibrous prostate is lower than might have been expected, while the proportion

TABLE I

Pathological Classification

Diagnosis.		Number.		Percentage.
Simple prostatic hypertrophy	. .	334	=	82
Chronic interstitial prostatitis	. .	22	=	5
Carcinoma	. .	50	=	12
Total	.	406		

of those with carcinoma conforms more or less with that usually quoted.

SIMPLE PROSTATIC HYPERTROPHY

Turning to simple prostatic hypertrophy in particular, Table II indicates the varying methods of treatment carried out in 334 cases and the mortality rate pertaining to each. It will be noted that in

TABLE II

Simple Prostatic Hypertrophy Average Age on Admission

Treatment	Number.	Died.	Mortality.	Average Age.	Youngest.	Oldest.
			Per Cent.			
No operation . . .	6	6	100	65	59	70
S/P cystostomy only .	49	20	40·8	74	56	90
Two-stage prostatectomy .	169	18	10·6 } 9·6	67	52	87
One-stage prostatectomy .	110	9	8·2 }	65	51	78
Total . . .	334	53	15·8	...	...	...

Of 334 cases, 279 (83 per cent.) received radical treatment.
Of 218 cases drained S/P, 169 (77·5 per cent.) came to prostatectomy.

arriving at a total mortality rate there has been no selection of cases. All those admitted are accounted for and there are thus included 6 patients who were virtually moribund from uræmia when first seen and who died within a matter of hours after coming in. Similarly, of those whose only treatment was a suprapubic cystostomy, with or without preliminary catheter drainage, the majority were either desperately ill when admitted or so old and enfeebled as to preclude more than palliative treatment. Many were œdematous and breathless with failing heart and pulmonary congestion. All had retention or overflow incontinence. Several had been repeatedly catheterised at home and were bleeding or had gross infection. Most of those who died did so after only a few days, but in some the process was considerably slower. The age incidence in this section will be referred to later. To summarise, it will be seen that 17 per cent. of all cases were unfit for radical treatment.

Of the remaining 279 cases 169 required a two-stage prostatectomy and 110 were considered fit for the one-stage operation. Naturally the mortality rate of the two-stage method is the higher, in that these patients were the poorer risks, but the comparatively small difference between the two is a measure of the comparative safety of the delayed technique. The combined mortality rate of 9·6 per cent. closely compares with the figure of 9·07 per cent. quoted by Barrington for a five-year period in St Peter's Hospital, London, prior to the war.

The expectation of operability has been calculated to show that of the total cases, 83 per cent. were found fit for immediate or delayed prostatectomy, and of those patients who required preliminary cystostomy, 77 per cent. improved sufficiently to warrant subsequent removal of the gland.

Up to 1939 the numbers of one- and two-stage prostatectomies were about equal, with a preference for the former on technical grounds, provided no undue risk was envisaged. Since the start of the war the picture has changed in that the majority of patients seem to have been admitted late with complete retention or with a very gross amount of residual urine. Thus of 65 more recent cases, only 6 were considered fit for a one-stage prostatectomy. All of these patients recovered, while there were 4 deaths, representing a mortality rate of 6·8 per cent. in the remainder who were subjected to the two-stage operation. The condition of a further 10 patients precluded more than a palliative cystostomy being performed.

Age Incidence.—Table II shows the age of the patients in the four selected categories. On the whole, the average is between 65 and 67 years, except in those who were clearly only fit for palliative cystostomy. In the latter class, though some were comparatively young, the majority were in the eighth or nine decade of life.

Table III has been compiled to show the age incidence in five-year

TABLE III
Simple Prostatic Hypertrophy

Age Period.	One-Stage Prostatectomy.		Two-Stage Prostatectomy.	
	Recoveries.	Deaths.	Recoveries.	Deaths.
51-55	5	1	6	...
56-60	22	2	17	4
61-65	26	1	42	2
66-70	27	4	42	3
71-75	18	1	34	5
76-80	3	...	6	2
81-85	...	...	3	2
86-90	...	...	1	...
Total	101	9	151	18

periods with the numbers of one- and two-stage operations, and the relative mortality for each period. Most of the patients are between

55 and 75 years of age, with the greatest incidence between 60 and 70. The fact that in this series there were fifty-seven patients with ages ranging between 50 and 60 years seems sufficient cause for discarding the old term "senile hypertrophy," and it is significant that the only death in a patient under 55 years was due to a sudden pulmonary embolism in one whose progress up to that point had been quite satisfactory. At the other end of the scale there is evidence that advanced age in itself does not contra-indicate radical treatment. In fact, some of the more elderly subjects were actually better operative risks than some of the younger ones. As age advanced, however, the proportion of two-stage operations naturally increased.

DURATION OF PRELIMINARY DRAINAGE IN TWO-STAGE PROSTATECTOMY

One hundred consecutive cases were taken for comparison (Table IV), and these show an average period of 17 days between the two stages of operative treatment. In the majority of the more

TABLE IV
Simple Prostatic Hypertrophy

Duration of Preliminary Drainage in Two-Stage Prostatectomy
Average for 100 cases = 17 days.
12 Cases "delayed prostatectomy"—average 190 days. 2 died.
1 Case—One year ⎫
1 Case—Three years ⎬ Both recovered.

favourable cases the interval was usually from 10 to 14 days. In 14 cases prostatectomy had to be much longer delayed, the patients being sent home in the interval to recuperate. In 12 of these the average duration of drainage was 190 days, and only two died after the second operation, both owing to renal failure which resisted all measures, including intravenous sodium sulphate therapy. In the other two cases even more prolonged drainage was required—one year and three years—yet both men eventually did well. It would appear that the necessity for this so-called delayed action prostatectomy need not vitiate the final result, provided that the bladder can be kept reasonably clean and the catheter free from massive encrustation. Considerable care and attention is required for this, and it must be admitted that an intractable infection once established may defeat all efforts to control it.

HEALING OF THE SUPRAPUBIC FISTULA

It has been maintained that after a one-stage prostatectomy the vesical wound closes much more rapidly than after the two-stage

TABLE V
Simple Prostatic Hypertrophy

Average Stay in Hospital after Prostatectomy. All patients in same charge
One-stage prostatectomy . . . . 91 cases = 31·4 days
Two-stage prostatectomy . . . . 86 „ = 30 „

operation. Judging from the average post-operative stay in hospital in this series, it would seem that there is little if any difference. After either procedure it was about 30 days.

CAUSE OF DEATH AFTER PROSTATECTOMY

A. After One-Stage Prostatectomy.—Reference has already been made to the number of deaths in this series, 9 in 110 cases, representing a mortality rate of 8·2 per cent. Table VI shows the main facts in

TABLE VI

Simple Prostatic Hypertrophy

Deaths after One-Stage Prostatectomy. 110 Cases

Number of deaths 9		
Average age 64	Youngest . . 56 Oldest . . 73	
Time elapse after operation . . . Average 15 days (4 within 7 days)		
Blood urea nitrogen readings . . . Average 24 mgs. per cent.		

Cause of death :—

    2 cases, post-operative hæmorrhage and shock, one immediate, one after removal of pack
    1 case, gross pre-operative hæmorrhage—" emergency prostatectomy "
    1 case, pulmonary embolism
    1 case, sepsis-pyonephrosis
  *1 case, anuria commencing on 10th post-operative day
  *1 case, cardiac with myocardial degeneration and pulmonary œdema
  *2 cases, gradual renal failure.

<p align="center">* Preceding attacks of retention.</p>

regard to these fatalities. The average age of the patients was 64 years, and in all of them the urea readings in the blood were within the limits which are usually considered safe for such an undertaking.

In 3 cases, the cause of death was hæmorrhage and shock. Of these one was a primary hæmorrhage which was succeeded by anuria. In another, gross bleeding had been occasioned by catheterisation before admission, and this could not be adequately controlled when the bladder was opened and the clots were removed. An emergency prostatectomy, though easily accomplished, failed to save the patient's life. The third case was one of secondary hæmorrhage following the removal of a pack. The case of pulmonary embolism has already been alluded to. One death was due to gross sepsis, there being infection of the bladder, epididymitis and a suppurative infection in a previous hydronephrosis. There was one case of sudden anuria commencing on the tenth day, two cases of gradual renal failure, and one of myocardial failure. The histories of these last four men showed that there had been preceding attacks of urinary retention, which suggests that a two-stage technique might have been preferable.

B. After Two-Stage Prostatectomy.—Here there were 18 deaths in 169 cases, a mortality rate of 10·6 per cent.

Table VII shows that the average age was now raised to 69 and the average interval between the two operations was 30 days for 16

cases. This indicates that on the whole they were considered as serious despite the fact that the blood urea readings fell markedly as a result of drainage.

TABLE VII

Simple Prostatic Hypertrophy

Deaths after Two-Stage Prostatectomy. 169 Cases

Number of deaths . . .	. 18		
Average age . . .	. 69	Youngest . . 58 Oldest .	. 84
Time elapse after operation	.	Average 13 days (7 within 8 days)	
Period between the two stages . .	.	Average for 16 cases = 30 days	

Remaining 2 cases, 120 and 210 days

Blood urea nitrogen readings (available in 11 cases) :—
Average before cystostomy = 38 mgs. per cent.
,,   ,,   prostatectomy = 16 mgs. per cent.

Cause of Death

A. Preceding Contributory Factors.
  Gross retention . . . . 13 Cases
  Severe cystitis . . . . 2 ,,
  Sever bleeding . . . . 2 ,,

B. Immediate Cause of Death.
  Shock and collapse . . . 1 ,,
  Anuria . . . . . 3 ,,
  Congestive heart failure . . 1 ,,
  Gradual renal failure associated
    with cardiac and pulmonary
    disease . . . . . 3 ,,

B.—contd.
  Acute pyelonephritis . . 2 Cases
  Subacute pyelonephritis . . 2 ,,
  Thrombo-phlebitis . . . 1 ,,
  Lung abscess . . . 1 ,,
  Peritonitis arising locally . 1 ,,
  Perforated gastric ulcer . . 1 ,,
  Cerebral thrombosis . . . 1 ,,
  Cerebral hæmorrhage . . 1 ,,

Preceding contributory factors were gross retention, infection, and hæmorrhage, conditions which would naturally undermine resistance.

An analysis of the immediate causes of death suggests that infection, either local or remote, together with the effects of chronic back pressure were the most potent agents. Thus there were four deaths due to bilateral renal infection and six due to anuria. The hazards of old age are shown by the presence of concomitant cardiac and pulmonary disease, and by the occurrence of cerebral thrombosis and hæmorrhage. One case seems worthy of special comment. The patient was a man of 84 years of age who was admitted with urinary retention of six days' duration which had been treated by intermittent catheterisation. The urea nitrogen of the blood was found to be 20 mgms. per cent. which fell to 14 mgms. per cent. after three weeks' suprapubic drainage. He died three days after prostatectomy, and the post-mortem examination revealed well-marked polycystic disease of both kidneys, an interesting sidelight on our views of the course and prognosis of this congenital anomaly.

COMMENTARY

Certain conclusions can be drawn from the foregoing review of a series of patients afflicted with simple prostatic hypertrophy.

(1) This type of prostatic disease is by no means confined to the really elderly. Quite commonly it is met with as a progressive condition in the middle fifties or even before, and by the time the middle sixties are reached it may be in its very late stage of development.

(2) It will sooner or later cause serious or irreparable damage to the kidneys, which will in turn lead to grave effects throughout the other systems of the body. The damage to the kidneys is due to the back pressure and is greatly accelerated if infection is superadded.

(3) The early symptoms of prostatism should not be disregarded. Any patient developing them should be investigated urologically, and if repeated examinations show progressive prostatic enlargement with evidences of commencing obstruction, operative treatment should be advised so as to obviate the risks attending treatment in the later stages.

(4) When conditions permit, a one-stage prostatectomy is an eminently satisfactory operation which should show a very low mortality rate and complete and lasting cure of the ailment. If there is any doubt at all, the two-stage method should be adopted in view of its safety and because it does not markedly increase the duration of stay in hospital.

(5) Blood urea estimations are only of limited value, as they may give no indication of the measure of the renal reserve still available. If the reading is above the normal limit (urea 50 mgms. per cent. or urea nitrogen 23·3 mgms. per cent.) it indicates definite impairment of renal function, but if the reading is at or below normal the converse does not hold good.

(6) The chief immediate risks after operation are hæmorrhage which can usually be controlled, and renal failure which should rarely occur if the pre-operative treatment and investigation are adequate. Elderly subjects are liable to develop cardiac, pulmonary or cerebral complications which cannot always be avoided. Many patients of advanced years, however, stand the operation so well that it is justifiable to take a certain amount of risk with them. Fatal pulmonary embolism is not a common complication.

(7) Patients may require very prolonged drainage, up to a year or more, to fit them for prostatectomy.

MANAGEMENT IN THE LATE CASE

As a result of experience in the management and treatment of the relatively late case, certain principles have commended themselves as worthy of special mention.

A. Method of Decompression.—In the really advanced case or when, as not infrequently happens, a complete prostatic retention has come on to complicate some intercurrent illness, even a simple suprapubic cystostomy under local anæsthesia may be highly dangerous. Some form of catheter drainage per urethram is much safer, provided

the bladder can be gently lavaged at the same time. A satisfactory answer to this problem has been found in the institution of tidal drainage by which the bladder is continuously washed out by a mild antiseptic solution and the rate of decompression can be readily adjusted. At the end of a week cystostomy can be safely performed without the same risk of inducing anuria. Owing to congestion changes, however, it is sometimes impossible to introduce any instrument into the bladder, in which case one must risk the suprapubic route, employing of course slow decompression.

B. Fluid Intake.—An abundant fluid intake to flush through the kidneys provides a simple though potent urinary antiseptic, highly desirable in all cases. Unfortunately, in the early stages after drainage is established, the forcing of fluids by mouth may be impossible, and if it is persevered with the only result is to induce a state analagous to water intoxication with anorexia and vomiting, while the urinary output, instead of increasing, goes down steadily. The kidneys cannot cope with the extra burden, but if for a time the intake is fairly drastically reduced, just as in acute nephritis, the output may rise again and the fluid intake can then be progressively stepped up. Should the above method fail, there should be no delay in instituting intravenous therapy. Usually an isotonic solution of sodium sulphate (42·85 gms. to the litre) is employed. This is probably better given in amounts of half a litre at a time rather than as a slower continuous drip.

C. General Assessment for Prostatectomy—No patient should be subjected to prostatectomy until he is able to be up and about in the ward. His appearance when lying in bed may be most deceptive, the apparent well-being changing to obvious infirmity when he is up. He should be well stabilised as to pulse, temperature and urinary output, any evidence to the effect that he is still in the process of improvement being an indication to wait. A certain amount of turbidity in the urine is almost inevitable, but gross pyuria, especially when associated with a slightly irregular temperature and pulse, is a definite contra-indication to operative intervention, even when the function tests seem satisfactory.

ASSESSMENT BY INTRAVENOUS PYELOGRAPHY
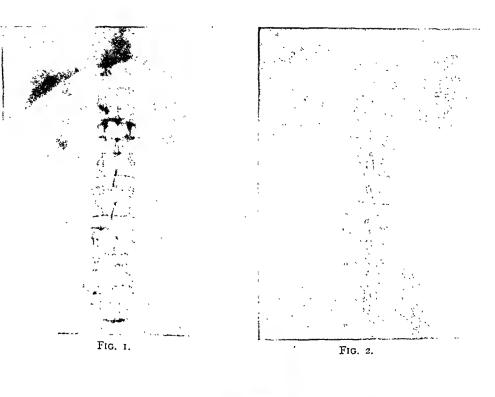
As a test of renal function in prostatic cases, intravenous pyelography has been found of special value as it not only provides a measure of function, but it also demonstrates very clearly the anatomical effects of back pressure. Three examples of its use may be quoted.
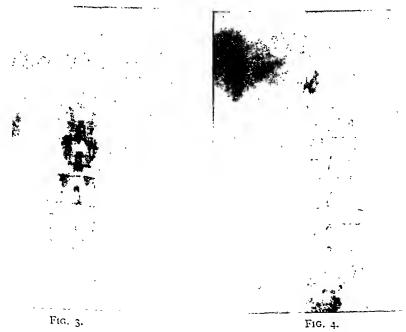
(1) W. R., aged 64. Seen three months before for simple prostatic hypertrophy with very little residual urine. Now admitted with 20 oz. of residual. Blood urea 48 mgs. per cent.. Intravenous pyelography (Fig. 1) showed good function in both kidneys with no hydronephrotic change. After a fortnight's drainage, prostatectomy was performed. A straightforward recovery ensued.

(2) D.P., aged 59. Seen three months before for simple hypertrophy. There was then 28 oz. of residual urine. Now admitted looking relatively well, but bladder grossly distended with residual urine. Blood urea 60 mgs. per cent. Intravenous pyelography (Fig. 2) showed very poor function and hydronephrotic changes in both kidneys. After 28 days' drainage the blood urea had dropped to 42 mgs. per cent. Intravenous pyelography (Fig. 3) now showed much improved function and considerably less hydronephrosis, but prostatectomy was delayed for a further fortnight, after which his progress was uneventful.

(3) A. T., aged 53. This man was admitted with a greatly distended bladder due to chronic retention. He was very ill and nearly died after a suprapubic cystostomy under local anæsthesia. The blood urea was 130 mgs. per cent. on admission and rose to 180 after cystostomy. Intravenous pyelography failed to show any shadow of a renal pelvis on either side even after thirty minutes. Drainage was continued for a year, at the end of which time the blood urea had fallen to 75 mgs. per cent. The general condition had so improved that prostatectomy was proceeded with and he made a good recovery. Four months later he returned to his work as a vanman. When reporting for a routine examination some eighteen months after prostatectomy, he was found to be looking not quite up to the mark. There was, however, no residual urine and the bladder was healthy on cystoscopic examination. The blood urea showed a reading of 86 mgs. per cent. and intravenous pyelography (Fig. 4) demonstrated impaired function and persistent hydronephrotic changes. The specific gravity of the urine was 1020 and it contained no pus cells or any abnormal chemical constituents. The blood pressure reading was 170/100. This follow-up examination accordingly indicated that in a man of only fifty-three years of age, prostatic hypertrophy had caused sufficient obstruction to lead to irreversible and permanent renal damage despite the complete relief of the obstruction.

Such cases as these well illustrate the contention that in simple prostatic hypertrophy we have a pathologically benign condition which is by no means confined to old age, is readily curable when treated reasonably early, but if neglected, will cause such vital injury that complete relief is problematical.

D. Follow-up Treatment.—It would be difficult to over-estimate the importance of a proper follow-up system in prostatic surgery. In hospital practice especially, where there is such pressure on bed accommodation, prostatectomy patients must often be discharged home as soon as natural micturition is established and they are able to be up for short periods. Most do well, but in the absence of any follow-up treatment there will be a certain proportion in whom trouble arises, and it is certainly not unknown for patients to require readmission to hospital on account of such serious sequelæ as retention, urinary fistula, or stone formation. There is little doubt that many of these gross complications, to say nothing of lesser afflictions, can be avoided if it is insisted that all patients must report back for an adequate examination some four to six weeks after leaving hospital whether or not their progress appears satisfactory. By this time the prostatic bed should be well on the way to healing

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

and the risks of instrumentation are therefore much diminished. Note is then made of any diminution in the size or force of the urinary stream, of progressive return of frequency, or of the presence of obvious pyuria. In actual practice the passage of a catheter, preferably of the semi-rigid rubber variety, may be all that is required. If a moderate sized instrument of this type can be readily introduced, and if there is little or no residual urine, one may be satisfied as to the result. Should there be evidence of a commencing stricture in the operation area, partial retention or pyuria, the need for regular attendance for urethral dilatations and lavage of the bladder is established. The correction of an early stricture may well obviate the necessity for a complicated reconstruction of the bladder neck at a later date, while the elimination of an infected residual urine should prevent the development of more or less serious vesical or renal sequelæ.

It can be concluded, therefore, that an efficient follow-up system for prostatic patients constitutes an essential adjunct to operative treatment and should never be neglected in any proper scheme of management.

THE ASSESSMENT OF SENSORY DENERVATION AFTER INJURIES OF PERIPHERAL NERVES *

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THE testing of sensation necessarily remains the least objective of methods of examination. We have no mechanical apparatus comparable to the square-wave stimulator (Ritchie, 1944) or to electromyography which will enable us to tell whether a given area of skin is sentient. Colorimetric sweating tests, measurements of skin resistance or records of vasomotor activity obtained by thermocouple or plethysmograph, may provide strong presumptive evidence of sensory denervation, but for scientific accuracy this is not enough. The development of the electro-encephalogram may solve this problem.

At present methods of examination remain crude and are not standardised. To test the fundamental modalities of cutaneous sensation most clinicians use the light touch of a wisp of cotton wool or a camel-hair brush, the prick of a needle, and test-tubes filled with hot and cold water. Those more scientifically inclined employ von Frey's hairs, some form of " algometer " and copper rods maintained at the desired temperature. All these methods possess the inherent drawback that the application of the stimulator to the skin causes deformation of the skin surface in addition to the excitation of the receptor which it is designed to stimulate. To overcome this difficulty, thermal sensation has been tested by a beam of light, and recently Bishop (1943) has described an electrical apparatus which will stimulate single sensory spots on the skin by means of a high voltage low current spark discharge. These are the methods of the laboratory, but it is only by their application to the problems of clinical medicine that we may hope to advance our knowledge.

ANATOMY AND PHYSIOLOGY

The disturbances of sensation which follow injuries to the peripheral nerves are many and varied, and for their assessment a knowledge of the anatomy and physiology of the peripheral sensory pathway is essential. We may consider :—

(1) *The Receptors.*—Each of the primary modalities of sensation : pain, touch, cold, warmth and pressure, is subserved by a receptor which is specific for that sensation. Position sense as tested clinically is a compound sensation composed of sensations arising from receptors

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* Part of this paper was read before the Society of British Neurological Surgeons on 1st June 1945.

in muscles, tendons, ligaments and joints (the proprioceptors). Morphologically, sensory end-organs are divided into two groups: (a) undifferentiated naked or beaded nerve endings and plexuses. These endings are ubiquitous and are exceedingly numerous in the epidermal and dermal layers of the skin. They are believed to subserve pain. (b) Highly specialised nerve endings such as the corpuscles of Meissner (Fig. 1) and Ruffini, the end bulbs of Krause and the Golgi-Mazzoni bodies. Each of the receptors in this group is believed to subserve a specific modality of sensation (Table I). When a

TABLE I

Relationship of End Organs and Nerve Fibres to the Modalities of Sensation

Sensation.	Receptor.	Fibre Type.	Fibre Group.
First (fast) pain	Free " beaded " nerve endings	Fine myelinated ($>$cold)	B
Second (slow) pain	Free " beaded " nerve endings	Unmyelinated	C
Warmth	? Ruffini's corpuscles	Fine myelinated ($>$cold)	B
Cold	Krause's end bulbs	Fine myelinated ($<$warmth and 1st pain)	B
Touch	Merkel's discs Meissner's corpuscles Hair root endings	Large myelinated	A
Pressure	Golgi-Mazzoni bodies Paccinian corpuscles	Large myelinated (15-18 μ)	A
Position sense (Pro-prioceptors)	Muscle spindles Golgi tendon organs Paccinian corpuscles	Large myelinated (18 μ)	A

Data from Fulton (1943).

specialised receptor is stimulated the sensation which is evoked is that specific to the receptor concerned irrespective of the nature of the stimulus; e.g. the insertion of the point of a sharp needle into a Meissner's corpuscle will produce a sensation of touch only (the doctrine of specific nervous energy).

Correlation of these findings with the punctate nature of cutaneous sensibility has shown that each sensory spot consists of two or more specialised receptors each innervated by a separate myelinated nerve fibre. The terminal branches of the peripheral nerves ramify deep to the skin, forming the superficial and deep cutaneous plexuses. The finer branches of these plexuses enter the superficial layers of the skin where they interlock with one another to form a nerve net with beaded terminals—the pain receptors. The larger fibres do not branch but run directly to the specialised receptors which are disposed in groups in the skin in a three-dimensional manner. For example, a single touch spot (say in a finger) consists of at least two Meissner's corpuscles innervated by separate nerve fibres which approach it from different directions. This multiple innervation of sensory spots provides for the recognition of graded stimuli and the ability to

localise accurately the site of the stimulus.   If the innervation of the
sensory spot is reduced without complete denervation, as may happen
if the spot is situated in the territory of an incompletely divided nerve
or in the zone of overlap of two adjacent peripheral nerves, one of
which is divided, or during the process of nerve regeneration, then the
ability to recognise gradations of stimuli and to localise accurately
may be lost although the essential quality of the sensation remains.
In addition to its main myelinated fibre each receptor receives an
accessory unmyelinated nerve fibre.   The purpose of this may be to
act as a sort of " burglar alarm " by evoking the sensation of pain
when the stimulus reaches a level which may be harmful to the
organism (Walshe, 1942).

(2) *The Peripheral Nerves.*—Anatomically peripheral nerves consist
of an aggregation of nerve fibres of varying sizes supported in a
framework of non-neural tissue (Fig. 2).   Many of these fibres are
efferent (motor and autonomic) and do not concern us ; the remainder
are afferent (sensory) fibres that enter the spinal cord *via* the dorsal
roots and are connected peripherally with the receptor organs.   The
dorsal roots contain both myelinated and unmyelinated fibres.
Physiologically fibres in the peripheral nerves are classified in three
groups (A, B and C) according to the type of action current which is
recorded from them by the cathode-ray oscillograph.   Correlation
between anatomical and physiological data shows that there is a
definite relation between fibre size and electrical conductivity.   " A "
fibres are rapidly conducting (approximately 100 m/sec.) and cor-
respond to large myelinated fibres, " B " fibres conduct more slowly
(10-30 m/sec.) and are more finely myelinated, and " C " fibres have
the slowest rate of conduction (0·5-5 m/sec.) and are non-myelinated.
The several modalities of sensation are each subserved by a specific
size of fibre.   The most highly specialised receptors (muscle spindles,
Paccinian corpuscles and Meissner's corpuscles) are connected with
large fibres belonging to the " A " group, while the free nerve endings
which subserve pain are associated with the slower conducting fibres
of the " B " and " C " groups (Table I).   It is now well recognised
that there are two modalities of pain.   The application of a needle
to the skin causes an initial, abrupt localised flash of pain followed
after an interval by a second pain which is rather diffuse, of greater
intensity, burning in quality and which fades slowly.   These sensations
are referred to as first (fast) pain and second (slow) pain.   There is good
evidence that these two types of pain are the result of different rates
of conduction in the nerve fibres which carry the pain impulses ;
first pain is carried by fibres of the " B " group and second
pain by those of the " C " group.   For accurate localisation of a
painful stimulus the " B " fibres are essential.* · Fibre size has another

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* A review of recent work (Gasser, 1943) which I have consulted since this
paper was read, casts considerable doubt upon the hypothesis that each modality of
sensation is associated with a specific group of nerve fibres.   (R. L. R.)
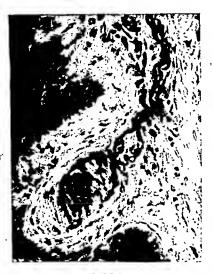
FIG. 1.—Normal Meissner's corpuscle from the skin of a finger. ×420. Weddell's neurofibril stain, counter-stained carmine.
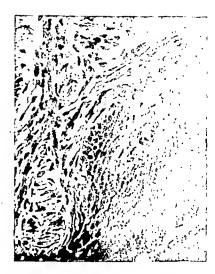
FIG. 3.—Abnormal Meissner's corpuscle from the skin of an index finger 5 years after an injury to the median nerve. ×450. Hortega neurofibril stain.
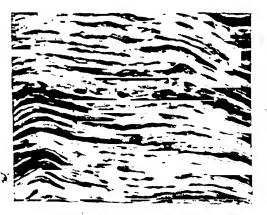
FIG. 2.—L.S. normal digital nerve. ×480. Hortega neurofibril stain.
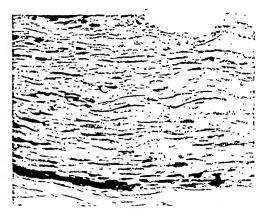
FIG. 4.—L. S. digital nerve to index finger 5 years after an injury to the median nerve. ×450. Hortega neurofibril stain.

important relation to peripheral nerve injuries. The vulnerability of the various types of fibre to different forms of trauma is directly related to their size and rate òf conduction. Thus large myelinated fibres are the most susceptible to pressure and asphyxia while small non-myelinated fibres are more readily affected by cold and cocaine (Table II).

TABLE II

Effect of Various Forms of Trauma upon Nerve Fibres and the Modalities of Sensation

Cocaine.		Pressure and Ischæmia.		Cold.	
Fibres.	Sensation.	Fibres.	Sensation.	Fibres.	Sensation.
Small fibres ↓ Large fibres	Cold Warmth 2nd pain 1st pain Touch	Large fibres ↓ Small fibres	Proprioceptive sensation Touch Cold Warmth 1st pain 2nd pain Deep pressure pain	No record ,, ,, ,, ,,	Cold 1st pain Touch 2nd pain Warmth

Data from : Gasser (1935) ; Lewis and Pochin (1938) ; Bickford (1939).

(3) *The Nerve Impulse.*—Effective stimulation of an end organ causes it to initiate impulses which are conveyed to the central nervous system along the nerve fibre with which it is connected. The end organ obeys the all-or-nothing law, and the type of impulse which travels up the nerve fibre is specific and unvarying so far as that particular fibre is concerned. It follows that the only way in which the intensity of a given stimulus can be conveyed to the central nervous system is either by an alteration in the frequency or total duration of the impulse discharge, or by the excitation of additional adjacent receptors of similar type. It is found that stimulation of a single receptor affects all other receptors which are innervated by the same parent nerve fibre so that their threshold for stimulation is lowered. This has given rise to the hypothesis that the sensory unit is not a single end organ and its afferent nerve fibre, but a single dorsal root fibre and all the receptors which it innervates, a conception analogous to Sherrington's motor unit, a single anterior horn cell and the muscle fibres which it innervates. Such a unit is represented by an area of skin of macroscopic proportions (rabbit's cornea 50-200 sq. mm. (Tower, 1940)).

(4) *Nerve Regeneration.*—After interruption of a peripheral nerve the axons distal to the site of the lesion undergo Wallerian degeneration. The supporting structure of the nerve remains intact except at the site of the lesion where, depending upon the nature of the trauma, it

may or may not be disrupted. In the former instance (neurotmesis *)
neuroma formation occurs. A neuroma is composed of nerve fibres
and proliferated Schwann cells from the central stump. If the divided
ends of the nerve are in close apposition, then outgrowing axons may
find their way through the neuroma and into the peripheral stump
where they enter Schwann cell tubes. The chances that such an axon
will reach its own particular Schwann cell tube are remote. Even after
suture, when the best possible apposition of the divided ends is attained,
the most that can be expected is that the axon will find its way into a
tube which will lead it to a receptor similar to that which it innervated
previously. Any fibres which do not do so are functionally useless and
atrophy from disuse. The chances of an axon finding its way to the
proper type of receptor are much greater in " pure " motor or sensory
nerves (radial or medial cutaneous) than in mixed nerves such as the
median or sciatic. The result of suture is inevitably a reduction in
the number of functional axons in the peripheral stump, and this in
turn results in a reduction in the number of innervated receptors in
the peripheral territory of the sutured nerve. Furthermore, these
innervated receptors will be supplied by different fibres from those
which formerly carried their impulses (*e.g.* after a median nerve
suture a Meissner's corpuscle at the tip of the index finger may be
innervated by a fibre which formerly connected with a similar receptor
in the palm). If, however, the non-neural framework has not been
distorted by the trauma which interrupts the axons (axonotmesis)
then each nerve fibre will regenerate along its own Schwann cell tube
and eventually reach its former end organ. Once receptor and nerve
fibre are again connected anatomically, they are not immediately
capable of functioning. During the period of denervation changes
have taken place in the end organ and the nerve fibre is not yet fully
mature. If there is prolonged denervation of the peripheral stump,
the Schwann cell tubes shrink and full maturation of the regenerating
fibres is impossible (Fig. 4). The neuro-histology of skin which is in
the process of re-innervation shows many atypical bizarre types of
end organs (Fig. 3). The first impulses which such a unit will convey
to the central nervous system must be abnormal and will be
manifest clinically by abnormal sensations. The rate of regeneration
of sensory nerve fibres in man has been calculated from the advance
of sensation over a denervated area. Data obtained in this way give
a figure of slightly more than 1 mm./day (Seddon *et al.*, 1943). It
must be realised that this is not a rate of growth nor a rate of full
functional completion, but represents the rate of regeneration of fibres
sufficiently mature to conduct some form of impulse.

* The classification of nerve injuries adopted in this paper is that suggested by
Seddon (1942, 1943).

CLINICAL OBSERVATIONS

(1) *Sensory Findings after Complete Division.*—After complete division of a peripheral nerve, all the receptors which it supplies will be cut off from the central nervous system. From what has been said above it will be apparent that the result will be the total denervation of some sensory spots and the partial denervation of others. The clinical result is an area deprived of all forms of sensation (the autonomous zone) surrounded by an area in which there is diminished sensation (the intermediate zone). Together these two areas make up the maximal zone of supply of any given peripheral nerve. The areas of total loss of the different modalities of sensation are not of the same size, but overlap one another concentrically (except in
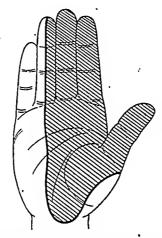
FIG. 5.—Normal cutaneous distribution of the median nerve in the palm.
(Redrawn from Stopford (1930).)

lesions of the brachial plexus). In nerve trunk lesions the area of loss of pain is less than that for touch, but in root lesions the converse is the case. As a rule, cold occupies an intermediate position between pain and touch, and warmth has the largest area of loss. If the anatomical boundaries of the area supplied by any given peripheral nerve are known, it ought to be a simple matter to assess sensory denervation in terms of the completeness or otherwise of nerve division. Thus far the problem is simple. A limited clinical experience is sufficient to dispel any illusions regarding the constancy of the sensory territory of a given nerve. Let us consider the distribution of the median nerve in the palm—probably the most important cutaneous receptive area in the body. The standard anatomical diagram of the normal cutaneous distribution of the median nerve is as shown in Fig. 5. From a series of cases of known complete division of the median nerve, the following have been selected as being representative of division of the nerve at three common sites of injury (Fig. 6):

A

D.M. 6·4·45.   R.H. 14·1·43.

B

H.S. 30·4·43.   R.P. 22·7·43.

C

////· Loss to Light Touch

####· Loss to Pin-Prick

J.W. 25·8·44.   K.M. 8·5·45.
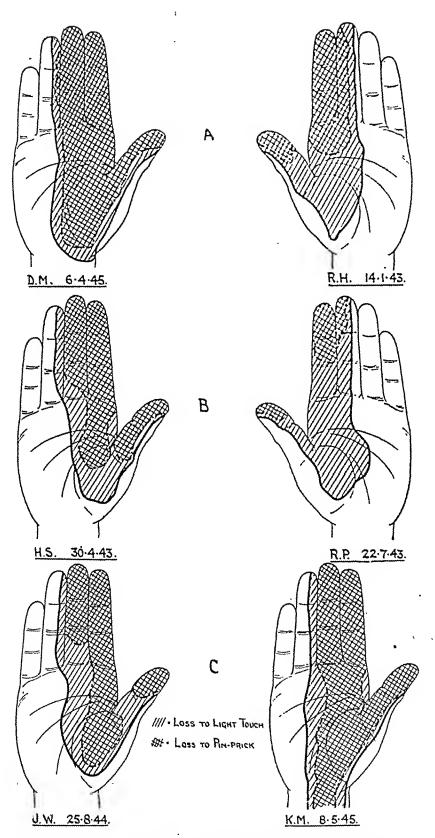
FIG. 6.—To show loss of sensation in 6 cases of division of the median nerve.
(See text for details.)

(A) in the arm before it has given off any branches ; (B) in the upper forearm below the proximal muscular branches but above the origin of the anterior interosseous nerve ; and (C) at the wrist where, apart from the branches to the thenar muscles, the nerve consists of sensory fibres only. It will be seen that few of these charts correspond to the standard diagram and that all are different. Anyone familiar with the standard diagram encountering Case RP might be forgiven for assuming that the patient had an incomplete or recovering nerve lesion, yet the nerve was found completely divided under pronator teres and the ends were more than one inch apart. The area of sensory loss depends upon the individual nerve and cannot be correlated with the level of the lesion ; large and small areas are found after both high and low division of the nerve. The median nerve is an extreme example of this variability in peripheral distribution, but it is shown by all peripheral nerves, although the nerves of the lower limb are on the whole more constant in their distribution than those of the upper limb. It follows that in making any assessment of the completeness of nerve division, one must rely not only upon the total area of loss of sensation, but upon the quality of that loss and in particular upon the lack of signs which indicate incomplete division or regeneration of nerve fibres. Even then, if we rely upon sensory findings only, we may fail, for reasons that will be explained presently, to diagnose correctly the nature of the lesion.

(2) *Sensory Findings after Incomplete Division.*—Incomplete division of a peripheral nerve may be of two types : (1) there may be a partial section of the nerve (partial neurotmesis), or (2) there may be interruption of certain axons in the nerve, although to outward appearance the nerve is normal (axonotmesis). Forms of trauma which may produce the latter result are pressure, ischæmia, the passage of a missile through or close to a nerve trunk, and cold (as in immersion foot).

In a straightforward case of the first type the sensory findings are exactly similar to those which follow complete division, but unless all the afferent fibres are in that portion of the nerve which is divided, only a portion of the total peripheral distribution of the nerve will be affected. The separation of cases in this group from those where there is complete division of a nerve with a small peripheral territory is difficult. It is in the investigation of cases of this nature that procaine nerve block has an application (Highet, 1942). If, after blocking the affected nerve, the area of sensory loss is increased, or if after blocking all the adjacent nerves sensation is still present within the maximal zone of supply of the injured nerve, then incomplete division may be diagnosed. The majority of cases of this type are associated with a hard neuroma which frequently requires excision ; after operation the area of sensory loss is increased.

Generalised diminution of all modalities of sensation within the territory of a peripheral nerve is another indication of incomplete

nerve division. Perhaps the commonest example of a lesion producing this effect is traumatic ulnar neuritis; the degree of sensory defect varying from minimal hypæsthesia and hypalgesia to almost complete sensory loss.

A dissociate type of sensory loss is another sure indication of incomplete nerve division. Depending upon the nature of the trauma, some nerve fibres suffer more severely than others. In pressure palsies (neurapraxia) where the essential lesion has been proved to be a demyelination of large fibres (Denny-Brown and Brenner, 1944), there is frequently no objective sensory loss. At most the patient will complain of subjective numbness or paræsthesiæ in the territory of the affected nerve, and there may be some defect in position sense. This is correlated with the' anatomical connexion of the receptors responsible for position sense with rapid conducting fibres of large calibre. In such cases recovery is rapid since Wallerian degeneration does not result. The passage of a missile through or close to a nerve trunk may cause a similar dissociation but with a much slower rate of recovery, *i.e.* certain axons have been completely interrupted (axonotmesis).

Pte. D. B. was wounded on 29.7.43. A grenade exploded at close range and some of the fragments peppered the left forearm just below the elbow.
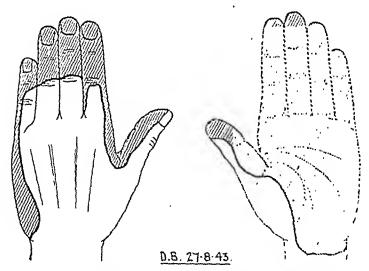
FIG. 7.—Case D.B.   To show area of cutaneous anæsthesia.

Sixteen days after the injury examination revealed paralysis of all the small muscles of the hand and loss of touch over the full cutaneous distribution of the median and ulnar nerves (Fig. 7). The response to pin prick was not altered in any way. Position sense was impaired but not entirely lost at all joints of the fingers. Unfortunately thermal sensation was not tested. Vasomotor activity was normal and there was slight hyperhidrosis of the palm of the hand. Radiographs of the elbow region showed numerous very small metallic foreign bodies in the soft tissues. Four months later recovery had commenced in the small muscles of the hand; cotton-wool touches were still

not appreciated over the palm, but slightly heavier touches were felt in the proximal part of the previously denervated area. The response was slightly " explosive " in character but localisation was fairly accurate.

Prolonged ischæmia causes a characteristic type of sensory disturbance. There is a " glove," " gauntlet," " stocking " or " slipper " area of sensory loss. Frequently the loss of sensation is not absolute. It is found that pressure stimuli or pin prick if applied with a little more force than usual will, after a slight delay, evoke an unpleasant, distinctly painful response which usually causes the withdrawal of the limb. Occasionally a burning quality is attributed to the sensation. The site of stimulation is not accurately identified.

In July 1944, L./Cpl. K. B. had a medial meniscotomy performed. A tourniquet was applied during the operation which lasted thirty minutes. After operation there was some swelling of the knee and he complained of severe pain in the foot. At this time the bandages were not removed, but when this was done later there was evidence in the form of pressure sores that there had been considerable pressure on the popliteal fossa. This unfortunate sequence of events resulted in a typical ischæmic paralysis. Five months after operation the sensory findings were as shown in Fig. 8. The stippling indicates the area from which a delayed pain response could be elicited.

These findings have been correlated by Parkes (1944) and others with the fact that the unmyelinated " C " fibres which subserve slow pain are the most resistant to asphyxia. A similar type of sensory dissociation is seen in immersion foot in which cold as well as ischæmia may damage the nerve fibres. Ischæmia may affect a single nerve trunk (e.g. the median) and in that case the typical findings will be confined to the territory of that nerve.

Persistent hyperæsthesia and hyperalgesia which are usually accompanied by spontaneous pain or paræsthesiæ almost invariably indicate an incompletely divided nerve. Spontaneous pain and hypersensitivity in the territory of a completely divided nerve have been described (Trotter and Davies, 1909 ; Schafer, 1928), but are transient phenomena and disappear after five or six weeks.

To summarise, the sensory findings in a case of incomplete division may be (1) loss of sensation in an area which is smaller than the autonomous zone of the nerve ; (2) general diminution of sensation in the maximal zone of the nerve ; (3) a dissociate type of sensory loss ; or (4) perversion of sensation.

(3) *Sensory Findings during Recovery.*—Recovery of sensation in a denervated area may be the result of any one of three processes :—

(i) Nerve fibres from adjacent nerves which supply the intermediate zone are not always able to function immediately after nerve division, but become able to do so within a few days. The importance of these fibres in relation to the early return of pain sensation after injury of the peripheral nerves was first pointed out by Pollock (1920).

(ii) In addition to the resumption of function by pre-existing fibres of adjacent nerves, there may be an ingrowth of fibres from these nerves into the autonomous territory of the divided nerve. It is thought that this growth of fibres is a manifestation of the continual degeneration and regeneration that take place normally in the cutaneous nerve plexuses (Weddell and Glees, 1941).

Together these two processes are responsible for the concentric shrinkage of the area of sensory loss that may be observed within the first fourteen days after nerve division.
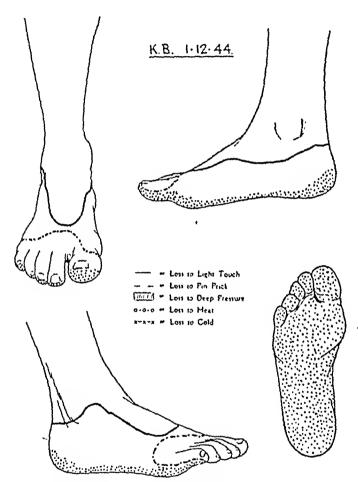
FIG. 8—Case K.B.   Diagram illustrating the sensory findings.

(iii) The regeneration of nerve fibres down the trunk of the injured nerve. This is the process which is responsible for the greater part of the sensory recovery and upon it the functional result of a nerve injury depends.

The sensory phenomena associated with nerve regeneration following suture were very fully described by Trotter and Davies (1909, 1913). The excellence of their clinical description is such that while the investigations of the last thirty years have added much anatomical and physiological data bearing upon the interpretation of these

phenomena, little or nothing has been added to their fundamental observations. Trotter and Davies showed that recovery commences at the proximal limit of the denervated area and spreads centrifugally. This is true for nerves that have large territories situated in the acral portions of the limbs, but is not true of nerves like the circumflex which supply a circumscribed area in the proximal part of a limb. In the latter case the area of sensory loss is found to shrink concentrically. The reason for this is that axons entering the denervated area from the main nerve trunk reach it first in areas adjacent to normally innervated skin (Weddell, 1942). Re-innervation of a full thickness skin graft also proceeds in this manner ; fibres grow into it from the adjacent peripheral nerves so that the area of sensory loss undergoes concentric shrinkage. Trotter and Davies described three characteristics of sensation during the phase of recovery : (1) a higher threshold of stimulation is required to elicit the sensation ; (2) the sensation is intensified ; and (3) it is referred peripherally. We may consider these abnormalities in turn. The raised threshold for stimulation means that if a method of stimulation of constant intensity is employed, one may fail to note that recovery has occurred. This accounts for the common observation that pain recovers before touch. Pain is normally a sensation with a variable threshold value, and the method of testing by pin prick is a very variable stimulus. The light touch of a wisp of cotton wool, on the other hand, is a relatively constant stimulus, and except on hairy parts it is possible for a considerable measure of recovery to touch to have occurred before it is detected by testing with cotton wool. If graded von Frey hairs are used it is found that after a good suture recovery of touch does in fact commence at the same time or very shortly after recovery of pain. Intensification means that the specific sensation when evoked is unusually vivid. This is most pronounced with sensations of pain and cold. Touch and warmth are not so markedly affected ; touch is a sensation not readily susceptible of intensification, and warmth when intensified tends to be felt as pain. Peripheral reference is the most striking of the phenomena of recovery. In the early stages of recovery, when only the proximal part of the denervated area is sentient, a stimulus applied to that area will be felt by the patient at the distal extremity of the area. In the case of a painful stimulus the referred sensation may be so vivid that the patient will rub the part to which it is referred (and, it may be added, obtain relief!). Peripheral reference is distinct in response to touch, cold or painful stimuli, but is difficult to elicit with warmth. Trotter and Davies also recognised the phenomenon of proximal reference. As recovery proceeds towards the central and distal parts of the denervated area, sensations may be referred not only distally but proximally, and even to a point outwith the denervated area, e.g. to the site of the nerve suture. Trotter and Davies do not mention " cross reference," but this also occurs, e.g. in a recovering median nerve lesion stimuli applied to the index finger may be referred

to the middle finger or thumb. During recovery the response to any stimulus is first an intensified referred sensation and later both an intensified local and an intensified referred sensation. After nerve suture these two phenomena (intensification and reference) are the most constant and persistent signs of regeneration and may be present for many years even after sensory acuity has reached a relatively high standard. Trotter and Davies suggested that peripheral reference was due to the stimulation of regenerating nerve fibres which had not yet reached end-organs and that intensification was the result of chronic irritation of these nerve fibres due to their unnatural contact with non-neural tissues. (An hypothesis which Trotter (1926) later expanded in his Victor Horsley lecture on " The Insulation of the Nervous System.") The return of local sensation indicated that the regenerating fibre had become reconnected with an end-organ. An acquaintance with modern views of the anatomy and physiology of the peripheral nervous system is sufficient to convince one that Trotter's views, attractive though they were at the time that they were formulated, are no longer tenable. The undifferentiated nature and universal distribution of the receptors for pain, the aberrant connexions that must result from the confusion of axons at the suture line and the bizarre receptors that are found in areas of skin during the process of regeneration, are in themselves sufficient to account for the clinical findings. The degree of recovery depends upon the interval between injury and suture and upon the technical excellence of the suture. Pain, subserved by undifferentiated nerve endings and relatively primitive fibres, has always a better chance of recovery than the other modalities of sensation and in some cases may be the only form of sensory recovery.

What has been said refers only to recovery after suture (neurotmesis). Trotter and Davies did not investigate recovery after a " lesion in continuity," but Sharpey-Schafer (1928) compared the results of division and suture of the digital nerve to the radial side of his left little finger with those of crushing the digital nerve to the ulnar side of the same digit. Crushing if not too severe produces a lesion in which the supporting structure of the nerve remains intact (axonotmesis) and each regenerating axon proceeds down its own Schwann cell tube to its previous receptor. There is no doubt about the quantitative difference between recovery after a lesion of this nature and that which follows even the best of sutures. In the former recovery approaches 100 per cent. ; thirteen months after the operation Schafer considered that sensation on the ulnar side of his little finger was normal. After suture recovery is always imperfect ; the finer grades of touch and thermal sensation, accurate localisation, two-point discrimination and stereognosis are never regained, and the phenomena of intensification and reference may remain. A qualitative difference during the phase of recovery might also be expected. During recovery from axonotmesis the phenomena of intensification and reference have also

been observed.   Schafer noted that hypersensitivity was less marked on the ulnar side of his little finger than on the radial side, but stimuli applied to the ulnar side during recovery were referred to the tip of the finger as on the side of the suture.   In clinical practice it is difficult to make a certain diagnosis of axonotmesis, but in observing sensory recovery in cases of peripheral nerve injury where the lesion was suspected to be of this nature, I have been impressed by the comparative absence of intensification and reference as compared with that which invariably follows suture.   The response to any form of stimulation often has a tingling quality and the site of stimulation is not located with great accuracy, but the patient usually indicates an area around the site of stimulation and states that he feels the sensation radiating from that point ;   a phenomenon that might be referred to as " local irradiation."   I believe that the phenomenon of reference is to be found only in cases in which there has been some crossing of axons at the site of the lesion (*i.e.* in cases of neurotmesis or partial neurotmesis), and I think it is probable that in Schafer's experiment the crush may have been sufficiently severe to have disrupted the supporting structure of the nerve to some extent—a view which is supported by the fact that a neuroma formed at the site of the crush.

In clinical practice any lesion which is accompanied by abnormal sensation in the territory of the injured nerve presents a problem in diagnosis.   When the phenomena of intensification and reference are present, it is a simple matter to be certain that one is dealing with a recovering   lesion.   It   may,   however,   be   extremely   difficult   to differentiate between complete division of a nerve that has a small autonomous zone and a large intermediate zone, and a lesion of the same nerve that is recovering following axonotmesis.   In both the intermediate and recovering zones a high threshold of stimulation is required, the response has an " explosive " quality and the site of stimulation is poorly localised because of " local irradiation."   The reason for this is at once apparent if we consider the problem from the anatomical aspect.   In both cases we have an area that is partially denervated ;   each sensory spot has less than its normal quota of innervated receptors, and those that are innervated are connected with their correct afferent fibre.   The sensory picture in the former lesion is static ;   in the latter steady progress will be observed.

It will perhaps occasion surprise that in this description of the phenomena of sensory recovery I have not referred to Head's (1920) experiment and his theories of " protopathic " and " epicritic " sensation.   Head's theories have been subjected to damaging criticism by Trotter and Davies (1909 ;   1913), Schafer (1928) and Walshe (1942), and they have not stood up to the test of interpretation in terms of the modern conception of the anatomy and physiology of sensation.   Head has few supporters among modern neurologists, and it were better that the terms " protopathic " and " epicritic " were forgotten.

I am indebted to Dr William Blackwood, F.R.C.S.E., of the Scottish Mental Hospitals Laboratory, for Figs. 1-4.

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POST-PRANDIAL VARIATION IN HÆMOGLOBIN

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INTRODUCTION

THE percentage of hæmoglobin in the blood of a healthy individual is usually regarded as one of the body constants, changing little, if at all, during normal activity. Some time ago my attention was drawn to a series of graphs which suggested that there was a definite variation in the value of hæmoglobin throughout the day. These were so striking that the question seemed worthy of further investigation.

Recent books on physiology and hæmatology which were consulted gave no information on this subject but, on referring to the earlier literature, I found that variations in the number of red blood cells and in the amount of hæmoglobin were quite well known.

Earlier reports by Reinecke (1889) showed variations in red blood cells of as much as a million and a similar change was recorded by Gustofsen and Benedict (1928). Ward (1904) suggested that the diurnal variation did not exceed 5 per cent. Dreyer *et alii* (1920) and Rabinovitch (1923) found that different readings of hæmoglobin taken throughout the day varied by 10 to 15 per cent. and occasionally even as much as 30 per cent. The highest values for red blood cells and hæmoglobin are said to be found during the waking hours, and there is a gradual decrease as the day advances (Reinert, 1891 ; Ward, 1904; Dreyer *et alii*, 1920, and Rud, 1922). Rud pointed out, however, that the red blood cells and the hæmoglobin in the same individuals showed no appreciable variation over several months if estimated always at the same time of day.

INVESTIGATION

In an endeavour to confirm or disprove the occurrence of a diurnal variation, the percentage of hæmoglobin has been estimated at hourly intervals on a series of patients in a general medical ward. An investigation of this sort demands an accurate and constant technique. The hæmoglobinometer used was the Haldane, the carboxyhæmoglobin solution of which was standardised with another Haldane hæmoglobinometer of known accuracy. The same technique and the same instrument were used during the whole of the investigation ; the source of illumination was always constant and all the observations were made by the same person under uniform conditions. In order to determine the standard of accuracy likely to be attained a number of successive estimations were made on each of several samples of

oxalated blood. The results showed that hæmoglobin estimations on any sample of blood could be obtained with a variation of plus or minus 2 per cent. For example, ten samples successively examined from about five cubic centimetres of an oxalated blood gave the following figures :—

82, 83, 83, 81, 84, 83, 82, 81, 83, 82 per cent.

This was considered a sufficiently accurate technique.

Hæmoglobin estimations were carried out on patients at hourly intervals from 10 a.m. to 4 p.m. The usual full hospital dinner of about 488 calories was served at 1 p.m. The patients were not allowed any extra food or fluid throughout the period of investigation. The hæmoglobin was estimated on blood removed from the cubital vein. The same volume of blood was withdrawn on each occasion and a constant amount of oxalate used for each sample. With practice it is easily possible to complete the withdrawal within thirty seconds, and the observations of Gray, Loutit, Marshall, Heck and Marwick (1945) have shown that arrest of the venous flow for this length of time does not affect the concentration of hæmoglobin. In a number of cases the estimations were repeated on the same patients several days later. McCarthy and Van Slyke, estimating hæmoglobin, found the greatest range of variation for the day to be equivalent to 11 per cent. of the mean Hb.
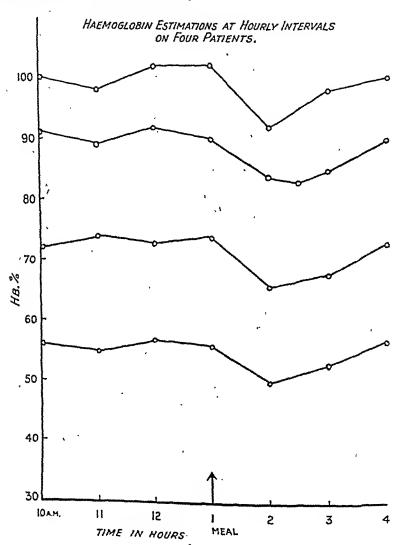
RESULTS

It was found that in all cases the hæmoglobin percentage remained fairly constant before the meal, but afterwards varied by an amount well outside the experimental error. This variation was in the majority of cases a fall and usually amounted to 8 or 10 per cent., and in a few instances to 12 per cent.

The fall was maximum about one to one and a half hours after the meal and in about three hours the hæmoglobin had returned to approximately the original reading. An endeavour was made to determine more accurately the time of the maximum fall by estimating the hæmoglobin every fifteen minutes after the meal. In all the cases the lowest point was reached between one and one and a half hours after the meal. The actual time of the maximum varied in different subjects. That the hæmoglobin may vary by as much as 10 per cent. throughout the day is a point which must be remembered when periodic examinations are required to test the progress of an individual.

The total number of cases examined was 41 and there was a post-prandial fall in the hæmoglobin in all but seven of these. In the smaller group of 7 cases the hæmoglobin rose after the meal. Five of these patients suffered from benign hypertension and two others were cases of hyperthyroidism. In no case examined did the values remain constant after a full meal had been taken. If these 7 cases are disregarded there remain 34 in which there was a fall in hæmo-

globin. In this larger group the difference between the mean values of hæmoglobin before and after the meal was 6·4 per cent., while the standard error of the difference between the means was 0·5. This is significant as the difference between the means is more than twice the standard error of the difference between them. The results obtained are shown on the accompanying graph. These findings confirm the fact that the percentage of hæmoglobin falls after a meal or, at least, falls at that time of day.

HÆMOGLOBIN ESTIMATIONS AT HOURLY INTERVALS ON FOUR PATIENTS.

In order to test the influence of the intake of food, the one o'clock meal was withheld from several patients, and others received much smaller meals. Under these conditions it was found that there was no significant variation in hæmoglobin, thus ruling out the existence of some cyclic change in the body. It can hence be stated that the fall in hæmoglobin would appear to be related to food intake, the

larger the meal the greater the fall. The midday meal in hospital is the largest the patients receive. Diabetic patients, who took a larger meal in the evening, showed a maximum fall in hæmoglobin after the heavier meal. The following figures of hæmoglobin estimated at hourly intervals are from a non-diabetic individual on different days (A) when a heavy meal was taken at 1 p.m., and (B) when the meal was taken at 7 p.m.

A.	Time .	.	10	11	12	1	2	3	4
	Hb .	.	96	95	97	97	90	93	95
B.	Time .	.	4	5	6	7	8	9	10
	Hb .	.	97	98	99	99	94	95	98

This post-prandial fall in hæmoglobin is in keeping with the findings of the majority of other investigators, although earlier observations on R.B.C. and hæmoglobin after meals had suggested that there was an immediate rise following the meal. Sörensen (1876) estimated the R.B.C. and hæmoglobin on his own blood and found that an hour after food there was a rise though this was succeeded by a fall maximum in about four hours. On the other hand, Vierordt (1852), estimating R.B.C. before and after the midday meal, found a fall two hours after the meal. Later he found that the hæmoglobin also showed the same variation. This work has been confirmed by Reinert (1891) and by Leichtenstern. The latter showed the value of hæmoglobin to be highest at 12 noon and to fall one to two hours after the midday meal. Von Limbeck (1896) also reported a post-prandial fall in hæmoglobin, but in his experience the decrease was maximum three to four hours after food. Oliver (1892) found lower cell counts following a meal, even when water was withheld.

Rabinovitch and Strean (1924), however, suggested that food intake had no effect on the variation curve of hæmoglobin throughout the day. Rud (1922), too, failed to show significant changes in R.B.C. and hæmoglobin following meals. Rabinovitch (1923) observed that in patients with advanced cardiac failure there was a marked fixation of the hæmoglobin curve, while Mills (1925) found a lessened variation in various anæmias. Dreyer et alii (1920) believe that the variations are closely connected with alterations in pulse rate, blood pressure, rate and volume of respiration and with fluid absorption and kidney excretion.

All these investigators agree that variations in the percentage of hæmoglobin do occur during the day, although the influence of food intake is only recognised by some workers.

DISCUSSION

Many suggestions have been offered to explain this phenomenon.

(a) *Alteration in Blood Volume.*—During digestion an outpouring of intestinal juices occurs and this would tend to cause a temporary hæmo-concentration rather than a fall in the hæmoglobin.

A temporary increase of blood volume may occur due to mobilisation of fluid from the tissue depôts. Post-prandial absorption of fluid from the alimentary canal would tend to dilute the blood and increase blood volume. Vierordt (1852) explained the fall in hæmoglobin in this way and added that during digestion there was an increase in the " flow of lymph." Leichtenstern held a similar view. The increase in hæmoglobin which he described as occurring just before a meal he attributed to " the loss of fluid into the alimentary glands," and the subsequent fall he explained as being due to absorption of fluid from the intestine. Oliver (1892) believed that the variations in hæmoglobin after food corresponded with fluctuations in " the digestive lymph wave," the R.B.C. and hæmoglobin being lower when the amount of fluid in the tissues was greatest, and vice versa.

(b) *Water Intake.*—The fall in hæmoglobin may result from dilution of the blood due to the intake of fluid. Some experiments have been done to test the influence of this factor.

Five pints of water were given to each of three patients and the hæmoglobin was estimated before and at intervals afterwards. There was a maximum fall in hæmoglobin of only 3 per cent. under those conditions. This hardly compares with the figures usually obtained after an average meal. Green and Rowntree (1927), however, report a rapid and progressive diminution in hæmoglobin concentration following the administration of large quantities of water by mouth.

It is well known that in both man and animals fasting is followed by an increase in R.B.C. and hæmoglobin. Hayem (1889) and Cabot (1897) found that a twenty-four hour fast resulted in a gain of 0·4 to 0·5 million R.B.C. Experimental dehydration in animals has been shown to produce an increase of R.B.C. and hæmoglobin. Marriot (1923) showed that the degree to which this occurs depends on the rapidity with which fluid is lost from the body. The absence of a post-prandial fall in hæmoglobin when food is temporarily withheld is quite in keeping with these observations.

A parallel series of estimations of corpuscular iron was made in a number of cases in order to see whether the post-prandial changes in hæmoglobinometer readings might be due to some physical alteration in the fluid. These observations showed for each individual an almost constant value of corpuscular iron before and after a meal. The method employed was that of Wong and it is doubtful whether this can be considered as accurate as a simple hæmoglobinometer examination, since the method involves a more elaborate technique and eventually depends on a colorimetric comparison. If the Wong

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results be accepted, the post-prandial changes obtained by the Haldane method cannot be due to alteration in blood volume or dilution of the blood. However, the fact that in cases of hypertension and hyperthyroidism, in both of which diseases the circulatory system is involved, there was a rise in the hæmoglobinometer reading would suggest that a change in blood volume may still be an explanation of the fall in the hæmoglobin.

Oliver (1896) has shown that any influence causing a rise in blood pressure will slightly concentrate the blood. Cabot (1897) states that a rise or fall in blood pressure may temporarily concentrate or dilute the blood by affecting the interchange of fluid between the vessels and the surrounding lymph spaces.

(c) *Digestive Leucocytosis.*—It was suggested by a hæmatologist that the changed hæmoglobin reading after a meal might depend on some altered refractivity due to the post-prandial leucocytosis. It would seem doubtful, however, whether the relatively small number of leucocytes involved would be sufficient to influence the hæmoglobin reading. A fortunate opportunity has made it possible to examine two cases of chronic myelogenous leukæmia, in whom the leucocyte counts were 60,000 and 340,000 respectively. After the usual midday meal a fall of 6 per cent. in the hæmoglobin was obtained in the first case and 5 per cent. in the second case. On a later occasion the corresponding figures were 8 and 6 per cent.

(d) *Changes in pH of the Blood.*—Price Jones (1920) showed that there was a diurnal variation in the diameter of the R.B.C., there being a gradual increase during the day and a diminution during sleep. He suggested that the R.B.C. swell and shrink in association with bodily activity. He found too that violent exercise increased these changes and that rest in bed did not entirely abolish them. He further stated that the variations in size and shape of the R.B.C. are due to differences in the reaction of the blood, the R.B.C. swelling in size with an increase of acidity and shrinking when the blood is made alkaline. The post-prandial fall in hæmoglobin cannot be due to alteration in refractivity produced by variations in size of the red cells, as they would be lysed at once by the distilled water used to dilute the sample.

Variations in hæmoglobinometer readings of the same sample of blood can be produced by varying the pH of the diluent as is seen in the following experiment :—The percentage of hæmoglobin was estimated on a sample of blood using (a) distilled water pH 7·0, (b) distilled water made alkaline to pH 8·5, and (c) distilled water made acid to pH 6·0 as the diluent fluids. No difference in the readings was obtained in (a) or (b) but the results were very variable in (c). The acid, of course, alters the colour of the blood to some extent and exact matching becomes more difficult.

An attempt has been made to carry out a somewhat similar experiment on patients. Potassium citrate, gr. 60, was given with

the meal and the hæmoglobin was estimated as before. This resulted in a more prolonged fall in the hæmoglobin which, instead of returning to its original value three hours after the meal, took four hours, although the time of maximum fall was the same. When a similar amount of potassium citrate was administered to patients at times when the hæmoglobin was known to be more or less constant, between 10 and 12 in the morning or between 7 and 9 in the evening, the percentage of hæmoglobin did not alter at all.

Parallel estimations of hæmoglobin and of the pH of the blood (by pH meter) were made. pH of the blood was estimated on ten samples of venous blood removed under paraffin before and after a meal. It was observed that, although the hæmoglobin fell as usual in every case, the pH bore no relationship to this fall and was, in fact, quite variable.

These results would suggest that the post-prandial fall in hæmoglobin was not due to any alteration in refractivity or to any variation in pH of the blood occurring at that time.

(e) *Exercise.*—It is the custom in the ward for all patients to remain in bed until the evening, when those who are fit are allowed to get up for a little. It was noticed that the hæmoglobin readings of samples of blood removed at 7, 8 and 9 p.m. were on the average 4 per cent. higher than those taken at 10, 11 and 12 in the morning, and that this occurred in patients who were ambulant during the evening. That active muscular exercise provokes an increase in the peripheral erythrocyte count has been known since it was reported by Hawk (1903). He found an average gain in R.B.C. of 21 per cent. after swimming and 12 per cent. after bicycling. Later investigators have confirmed these earlier observations. Schneider and Havens (1915) found that the immediate influence of physical exertion was to cause a concentration of the blood of the periphery, with 3·5 to 10·9 per cent. increase of hæmoglobin and 3·2 to 22·8 per cent. increase of red cells. These workers have further observed that massage of the abdomen or pressure over it will raise the content of hæmoglobin and R.B.C. in the peripheral stream. Boothby and Berry (1915), however, found that the percentage of hæmoglobin and R.B.C. only increased under conditions of work which caused an appreciable amount of perspiration, but not otherwise. Broun (1922) has published a series of instructive experiments on the effect of exercise on the blood of dogs. This worker measured the number of R.B.C., the hæmoglobin and the total blood volume. He found that after ten to fifteen minutes of active exercise there was a slight increase of plasma volume and quite a marked increase in hæmoglobin and R.B.C. After the work had been continued several hours the plasma volume was still increasing but the hæmoglobin and the R.B.C. now showed a decrease as compared with the figures obtained after fifteen minutes' exertion.

The effect of exercise was examined in a group of eight patients.

As a preliminary the hæmoglobin was estimated before and after the midday meal and the expected fall occurred as usual. The following day the morning estimations of hæmoglobin were repeated and immediately after the midday meal the patient mounted the ergometer and did work equivalent to cycling two miles. It was found that in every case the exercise abolished the expected post-prandial fall of hæmoglobin, any variation being within the limits of experimental error.

Broun (1922) showed that the initial concentration of blood during exercise is not due to loss of fluid as there is no decrease in the total volume of circulating blood, but is probably the result of a redistribution of the cells. Barcroft and his associates (1923) suggest that the chief source of the early supply of R.B.C. following exercise is probably the spleen. Scheunert and Krzykranek (1926) have found that the initial increase in the number of cells and hæmoglobin following exercise is absent in splenectomised animals. Since, therefore, exercise abolishes the post-prandial drop in hæmoglobin probably by redistributing red cells from the splanchnic area to the periphery, it is tempting to think that the post-prandial reduction in the hæmoglobin in a peripheral vessel is also due to an altered distribution of the R.B.C.

Adrenalin, which is known to cause contraction of the spleen, was given to a number of cases and the hæmoglobin was estimated at frequent intervals. It was found that there was a definite increase in the value of hæmoglobin outside the experimental error. When adrenalin was given to patients before the midday meal the hæmoglobin values either remained constant or were slightly increased at the time when the maximum post-prandial decrease should have occurred. This was found in every case examined. It would appear that under the action of adrenalin, contraction of the spleen and of the vessels of the abdominal viscera occurs leading to a redistribution of the cells to the periphery and that this would explain the elimination of the post-prandial fall in hæmoglobin. This is also suggested by recent investigations. Boycott and Jones (1922) found that ether anæsthesia caused an increase in the percentage of hæmoglobin in rabbits, and Hausner, Essex and Mann (1938) showed that ether anæsthesia caused a contraction of the spleen while sodium pentothal caused a dilatation. Finally, Pender and Lundy (1944) have found the hæmoglobin to fall in both dogs and man when under pentothal and to rise in both dogs and man when under ether anæsthesia.

SUMMARY

1. The percentage of hæmoglobin in the peripheral blood is not constant throughout the day.

2. There is usually a post-prandial fall in hæmoglobin of the order of 5 to 10 per cent. This fall is in proportion to the size of the meal—the larger the meal the greater the fall. There is also, presumably, a fall in the number of R.B.C. at this time. It will be

obvious that when periodic hæmoglobin values are required they should not be estimated within three hours following a large meal, or should be estimated at the same time of day, in order to avoid this post-prandial fall.

3. The possible cause of this decrease in hæmoglobin has been discussed. It is probably due to a redistribution of the cells from the periphery to the abdominal viscera and, possibly, also to slight changes in blood volume.

4. This fall in hæmoglobin can be prevented by exercise or by the administration of adrenalin.

5. Cases of hypertension and hyperthyroidism do not share this post-prandial decrease in hæmoglobin and further investigations are required on this subject.

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HÆMOLYTIC STREPTOCOCCI IN PUERPERAL SEPSIS

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HIGH vaginal swabs are sent to this Department from women showing pyrexia during the puerperium in order to determine whether group A hæmolytic streptococci are present, this group being the most virulent and the cause of hospital epidemics of puerperal sepsis and septicæmia.

Only 51 per cent. of the beta-hæmolytic streptococci isolated over a period of two years were found to be group A. The opportunity was therefore taken of determining the incidence of groups B, C and G streptococci in these cases, while beta-hæmolytic enterococci—whose antigens are similar to those of Lancefield group D—were also tested against D grouping sera.

These beta-hæmolytic streptococci, i.e. those showing a hæmolytic zone on blood agar plates, were tested also for soluble hæmolysin (using washed human cells), for fibrinolysin and as to their biochemical reactions.

One hundred strains from high vaginal swabs were isolated and examined, while the results obtained with 167 other beta-hæmolytic strains from various sources, chiefly throat swabs, are shown in the chart for purposes of comparison. The high vaginal swabs were taken from patients showing degrees of puerperal sepsis varying from trivial to severe.

METHODS

The high vaginal swabs were plated out on (human) blood agar plates and incubated overnight. Streptococcal colonies showing a zone of hæmolysis were subcultured on to laked blood agar (human blood was used in the preparation of this medium) and incubated for six hours and further subcultured in a 1 per cent. glucose trypsin broth, and in 10 per cent. serum peptone water. The resultant growth in the 1 per cent. glucose trypsin broth was centrifuged, and from the sediment an antigen was prepared for the precipitin test according to the Lancefield technique.

Fibrinolysin (Tillet and Garner).—Human plasma was obtained by collecting 5 c.c. of blood into a tube which had been previously prepared by evaporating 0·5 c.c. of a 2 per cent. potassium oxalate in the hot air oven. The blood was mixed by gently rolling the tube and centrifuging to obtain the plasma. For the test the following materials were mixed : 0·8 c.c. of N/1 saline, 0·2 c.c. of oxalated plasma, and 0·5 c.c. of the 10 per cent. serum peptone water culture ; coagulation was effected by the addition of 0·25 c.c. of a 0·25 per cent. solution of calcium chloride, and incubation in a waterbath at 37° C. The clot formed within a short time after the addition of the calcium chloride. Strongly fibrinolytic strains should dissolve this clot within fifteen minutes.

Hæmolytic Suspension.—Oxalated human blood was repeatedly washed with N/1 saline till a clear supernatant was obtained, and a 2 per cent.

suspension of the washed red blood cells was made in N/1 saline. For the soluble hæmolysin test 0·5 c.c. of the suspension was mixed with 0·5 c.c. of a 10 per cent. serum peptone water culture and incubated at 37° C. in a waterbath. The result was read after two hours.

Biochemical Reactions.—Hiss's serum water medium containing 1 per cent. of the various sugars was used with a 1 per cent. Andrade's solution as indicator.

RESULTS

Forty-eight per cent. of the 100 strains from high vaginal swabs proved to be group A, 16 per cent. group B, 10 per cent. group C, 8 per cent. group G, 9 per cent. group D, and 9 per cent. did not fall into any of these groups.

Group A.—In most of the cases yielding group A streptococci there was a heavy growth, and only 25 per cent. showed other organisms, staphylococci and *B. coli* being the most common. The zone of hæmolysis surrounding the colony was invariably large and well defined, and a soluble hæmolysin was produced with the human red cell suspension. All the streptococci isolated in this group were fibrinolytic, three hours being the average time taken to dissolve the clot. The majority of these strains fermented the usual sugars as shown in the chart, trehalose being fermented but not sorbite. Two strains, however, fermented both mannite and sorbite, and one fermented mannite but not sorbite. Starch and glycogen were fermented by 6 strains.

Group B.—Of the 16 group B strains only 56 per cent. showed a heavy growth, 63 per cent. being accompanied by other organisms. The zone of hæmolysis was very much smaller, only about 12 per cent. having a zone of hæmolysis comparable with those in group A, and all the strains failed to produce a soluble hæmolysin with the human red cells suspension. A sheep cell suspension, however, was hæmolysed to a considerable extent with all the strains. The fibrinolytic test was negative with all strains after eight hours, at which time it was arbitrarily terminated.

The lack of true hæmolytic and fibrinolytic activity suggests a low virulence for human beings, but these strains resembled the A group in fermenting trehalose but not sorbite.

Group C.—A good growth was obtained in 5 of the 10 cases, but only in 3 was there a pure culture. The zone of hæmolysis was very marked, in some instances being larger than those of group A, and occasionally (4 cases) the clear zone diffused into the surrounding medium giving the appearance of having a scalloped margin. A soluble hæmolysin was produced by all the strains, and only one was not fibrinolytic. The time taken to dissolve the clot was slightly less than that with group A. Biochemical reactions were again regular, trehalose being fermented and sorbite negative, suggesting that the strains were of human origin. Starch and glycogen were fermented by all the strains of this group.

Group G.—In 4 of the 8 group G cases a strong growth was

TABLE

Group	Source	Strong Growth	Pure Growth	Strong Haemolysis (Plate)	Haemolysis (Suspension)	Fibrinolysis	Dextrin	Galactose	Glucose	Glycogen	Inulin	Lactose	Maltose	Mannite	Mannose	Raffinose	Saccharose	Salicin	Sorbite	Starch	Trehalose	Gelatin	MacConkey's Medium
A.	48 HVS.	46	36	48	48	48	30	43	48	6	0	44	47	3	48	0	47	41	2	6	48	...	...
	88 Mis.	68	29	85	88	86	59	80	87	11	0	80	86	12	87	3	88	62	8	11	88	...	...
B.	16 HVS.	9	6	2+++ / 14+ / 1+++ / 2+	0	0	12	11	16	0	0	16	16	0	16	0	16	11	0	0	16	...	...
	3 Mis.	1	2		0	0	3	3	3	0	0	3	3	0	3	0	3	3	0	0	3	...	...
C.	10 HVS.	5	3	10	10	9	10	10	10	10	10	10	...	10	10	10	9	9	10	10	10	...	...
	6 Mis.	5	0	6	6	6	6	6	6	1	6	6	...	6	2	2	5	5	6	6	6	...	...
D.	9 HVS.	3	0+++ / 9+ / 4+++ / 4+	0	0	9	8	9	0	0	9	9	9	9	0	9	9	9	0	9	9	9	...
	8 Mis.	5		0	0	6	5	8	8	0	5	8	4	8	0	6	7	4	0	8	0	8	...
G.	8 HVS.	3	8	8	4	8	8	8	8	0	7	8	0	8	0	8	5	0	8	8	1	9	...
	1 Mis.	0	1	1	.	0	1	1	0	0	1	1	0	1	0	1	1	0	0	1	0	8	...
X.	9 HVS.	1	0+ / 9+ / 8+++ / 53+	0	0	8	5	9	3	5	5	5	4	9	4	8	8	4	2	5	1	...	0
	61 Mis.	1		0	0	36	56	58	2	10	47	40	2	58	24	61	19	1	6	11	0	...	...

HVS. = high vaginal swabs. Mis. = other sources. X group = not of groups A, B, C-D, or G.

obtained, and on three occasions the hæmolytic streptococcus was the only organism isolated. The zone of hæmolysis was similar to that of groups A and C. A soluble hæmolysin was produced in each instance. Only 4 of the strains, however, were fibrinolytic. The biochemical reactions were fairly constant, with starch and glycogen fermented on every occasion. Again trehalose was fermented but not sorbite.

Group D.—Enterococci were isolated on numerous occasions but only 9 showed an area of hæmolysis, which was never marked, surrounding the colony. In only 3 instances was the growth heavy and in one case a pure growth was obtained. A soluble hæmolysin was never produced by any of the strains. They all grew on MacConkey medium; gelatin was liquefied by one strain. Biochemical reactions were constant, mannite and sorbite being fermented by all the strains. The reaction with the grouping sera was very slow in appearing, three hours being the average time for the precipitate to appear.

Other Groups.—Nine strains did not fall into any of the above groups. Three of them yielded a good growth, which was pure on one occasion. The zone of hæmolysis was very slight; a soluble hæmolysin was never produced and the fibrinolytic test was also negative. They did not grow on MacConkey medium. The biochemical reaction varied considerably.

CONTROLS

Beta-hæmolytic streptococci from various sources but mostly from throat swabs are also included in the chart. Most of them reacted in the same way as the strains isolated from the high vaginal swabs. For instance the percentage of 12·5 of group A strains fermenting starch and glycogen was the same both in the control series and in those from the high vaginal swabs.

Group B Controls.—Only one strain of group B was isolated from a throat swab, that being from a scarlet fever contact. As the individual drank unpasteurised milk this would be the probable source. Further swabbing produced a group A streptococcus. The other 2 strains in this group were isolated from the genital tract.

Group C Controls.—Six throat strains all fermented starch and glycogen. One strain fermented inulin and sorbite as well as trehalose.

Groups G and D Controls.—All had the same characteristics as the high vaginal strains.

CLINICAL FEATURES

A clinical analysis is outwith the scope of this investigation, but details were obtained of the duration of stay in hospital of most of the cases. Many of the group A cases were transferred to the City Fever Hospital, as soon as it was known that their infection was of this kind; their transfer was not necessarily indicative of a severe

infection. Of the group B cases, one was transferred to the City Hospital and of another there was no record. Fourteen cases had an average duration in hospital, after the onset of fever, of 11 days. Group C, eliminating one sent to the City Hospital, and two with no record, had for 7 cases an average stay of 16 days. Group D, omitting one with no record, had an average stay of 12·5 days for 8 cases. Group G cases, with one to the City Hospital, had an average stay of 10 days for 7 cases. Of the cases yielding hæmolytic streptococci not falling into any of these groups, two had no record, and one was transferred to the City Hospital; the average stay of the remaining 6 cases was 6 days.

So far as this evidence goes, therefore, it suggests that group C infections were, after group A, the most severe, and the ungroupable streptococci the least severe; with groups D, B, and G cases occupying intermediate positions.

CONCLUSIONS

The formation of a soluble hæmolysin by the streptococci of groups A, C and G is evidence of the presence of an exotoxin, while the positive fibrinolytic test with 100 per cent. of the group A strains, 90 per cent. of the group C and 50 per cent. of the group G is proof of the invasive power of these strains.

The power of the groups C and G strains, like those of group A, to ferment trehalose and not sorbite is further evidence of their human origin. The fact that in 3 of the group C and 3 of the group G cases the growth of streptococcus was a pure one is corroborative evidence of ætiological connection between the organism and the condition of sepsis. The evidence for the pathogenicity of the groups B and D strains is not so strong, with an absence of a strong hæmolysin and of fibrinolytic activity. Nevertheless the presence of these strains in pure culture in six instances with group B and one with group D suggests that they may cause a lower grade of sepsis. One strain not falling into these five groups was also obtained in pure culture.

Fermentation tests with trehalose and sorbite are helpful in differentiating between " human " strains of groups B and G from those of animal origin. Starch and glycogen were found in this series to have a limited use in differentiating between group A and groups C and G.

While group A streptococci are the undoubted important bacteriological factor in severe puerperal sepsis and septicæmia, streptococci of groups B, C, D and G are also associated with an appreciable number of cases in which the sepsis is usually less severe. Of these, group C cases had the longest stay in hospital.

REFERENCE

TILLET, W. S., and GARNER, R. L. (1933), Journ. Exp. Med., 58, 485-502.

NOTE

A QUARTERLY meeting was held on 5th February 1946, the President, Dr D. M. Lyon, in the Chair. Dr D. M. F. Batty (Edinburgh), Dr J. Halliday Croom (Edinburgh), Dr G. A. G. Peterkin, M.B.E. (Edinburgh), Dr James Innes (Edinburgh), Dr Angus MacNiven (Glasgow), and Dr J. S. Fulton, C.B.E. (Glasgow) were introduced and took their seat as Fellows of the College.

Dr B. S. Bindra (Karachi, India) and Dr O. Olbrich (Edinburgh) were elected Fellows of the College.

NEW BOOKS

A History of Medicine. By DOUGLAS GUTHRIE, M.D., F.R.C.S. Pp. xvi+448, with 72 plates. Edinburgh: Thomas Nelson & Sons Ltd. 1945. Price 30s.

Many have felt that there is a need for a comprehensive short history of the Art and Science of Medicine and the author has been extremely successful in supplying this want. The story begins in prehistoric times, and carries the reader through early Greek and Hippocratic medicine, and by way of the Egyptian, Roman and Arabian schools to mediæval times. Then follows an account of the reformers and revolutionaries of the Renaissance, and the foundation of the earlier modern schools. With the appearance of scientific medicine progress has to be recorded in special departments and so the story is brought up to quite recent times. An interesting chapter is devoted to medical publications, and there is a valuable appendix on the bibliography of medical history.

The book is most attractively written and a judicious balance has been maintained between competing interests. The choice of illustrations has been excellent, but the medium in which they have been produced does not show them to the best advantage.

Dr Guthrie is to be congratulated on the result of his endeavour to produce a historical background to modern medicine; his history will undoubtedly have a good reception not only from the profession but also from the general reader.

Extensile Exposure Applied to Limb Surgery. By ARNOLD K. HENRY, M.B. DUBL., M.CH. CAIRO, F.R.C.S.I. Pp. 180, with 127 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 30s. net.

The somewhat curious title of this monograph is explained in the Preface, where the author states that he is describing surgical exposures that may be enlarged at will and therefore have a range, extensile, like the tongue of a chamelion, to reach where they are required.

The Introductory Chapter is most interesting and in it the author explains his use of anatomical terms which custom sanctions and which surgeons understand, even though they may not be in either of the three anatomical nomenclatures of the last thirty years. He thinks the time is ripe now for an agreed-on terminology which will be acceptable to those who work in living anatomy.

Thereafter all possible exposures in the arm and leg are very fully described, and in each case the anatomical route for extending it is detailed with such clarity that it can easily be followed.

The most delightful line and wash drawings illustrate the text and make its interpretation easy.

The author and artist are to be congratulated on a splendid production which one can see going into many editions. No less are the publishers to be congratulated, for rarely in recent years has such a beautiful book been issued.

Essentials of Allergy. By LEO H. CRISP, M.D. Pp. xv+381, with 43 illustrations. London : J. B. Lippincott Coy. 1945.

'The author points out that in dealing with this fascinating subject it is essential to secure a proper foundation and perspective, for there is to-day too much loose thinking, talking and writing about it. The earlier chapters deal with the fundamental facts, then follow others on diagnosis and treatment. The latter part of the book gives an account of the various allergic diseases.

The book has been written neither for the specialist in allergy nor for the patient, but it offers an admirable account of the subject for the practising physician.

Modern Treatment Year-Book. Edited by C. P. G. WAKELEY. Pp. viii+300, with 60 illustrations. London : Medical Press and Circular. 1945. Price 15s. net.

This volume consists of a series of forty-five informative articles which deal with many departments of medicine and surgery. It aims at bringing before the profession the latest accepted medical opinions. The articles are excellently written and well illustrated.

An admirable production which should be of the greatest service to the busy practitioner.

Facial Prosthesis. By ARTHUR H. BULBULIAN, M.S., D.D.S., F.A.C.D. Pp. 241, with 202 illustrations. London : W. B. Saunders Company Ltd. 1945. Price 25s. net.

During and since the last war the prosthetic method of facial reconstruction has received much attention, and this comprehensive guide will be most welcome and invaluable to surgeons and dentists interested in plastic repair. The subject matter is presented systematically, clearly and in detail. Chapters are included on the advantages and disadvantages of the rigid and flexible materials used in the construction of a prosthetic restoration, and on the facilities, instruments and supplies necessary for a well-equipped laboratory. A description of the methods of taking impressions and making casts is followed by sections dealing with the reconstruction of the nose, of the ear and of the orbit and eye. Although latex is the substance most frequently used in America, a chapter is devoted to plastics—the material employed in this country—and to the necessary colouring pigments. Photographs of selected cases are presented. The book is warmly recommended for its wealth of practical detail and helpful illustrations on the problem of facial disfigurement.

Principles of Internal Medicine. A course for Nurses. By D. M. BALTZAN, M.D., C.M., F.A.C.P., F.R.C.P.C. Pp. xvii+398, with 9 illustrations. Toronto : Ryerson Press. 1945. Price 25s. net.

This book has been written to cover the lectures required for the training of registered nurses, and is the result of considerable experience in this type of teaching. The object throughout is to explain the principles involved and not to make a catalogue of all the details of diseases. For further information the graduate nurse is advised to consult the regular medical textbooks. Treatment is described only in so far as it helps to further the explanation of the disease. It is recognised that practical medical nursing is best learnt at the bedside and no attempt is made to deal with it here.

The book is well written and excellently produced and should be of the greatest value to nurses in training.

Transactions of the American Gynecological Society. Volume 68 for the Year 1944. Edited by HOWARD C. TAYLOR, JR., M.D. Pp. lxvi+324. St Louis: C. V. Mosby Company. 1945.

This volume of Transactions contains the papers read at the Sixty-eighth Annual Meeting of the Society. These have already appeared in the *American Journal of Obstetrics and Gynecology* and are on a variety of clinical and pathological topics. The presidential address by Dr G. W. Kosmak on " Woman in this Changing World " reviews woman's accelerated arrival at her present new position—social, economic and even physical—in relation to her unalterable physiological and biological status. A dissertation by Dr Daily on " Maternity Care in the United States— Planning for the Future " and the subsequent discussion is of special interest in view of the plans under consideration for a Maternity Service in this country. The names of eleven distinguished American gynecologists, several, including Howard Atwood Kelly, with international reputations, appear in " In Memoriam."

Guide to Medical Practices. By RAMSAY BROWN, C.A. Pp. 96. London: H. K. Lewis & Co. Ltd. 1946. Price 5s.

The writer claims that he has had the opportunity of investigating many medical practices and the experiences of his many medical friends. His aim in producing this book is to compare medical practices from the financial point of view and to deal with the various problems which may arise when a doctor commences in practice. He points out how important it is that no doctor should purchase a practice without full investigation by an accountant or without legal advice.

The book is a mine of useful information and should be studied by all who are contemplating setting up in practice.

Biological Actions of Sex Hormones. By HAROLD BURROWS. Pp. x+514. Cambridge University Press. 1945. Price 42s. net.

Dr Burrows has written a comprehensive review of the actions of gonadotrophins, androgens, œstrogens, progesterone-like substances and the sex hormones of the adrenal cortex. As the author says, it is a general portrayal rather than a full and inclusive discussion, and some good work done in foreign lands has been given inadequate consideration.

At the same time, the book does deal systematically with the experimental work done with these substances. It makes reference to some 2000 published papers and makes excellent use of tables to illustrate various findings. Though it does not set out to stimulate discussion it is an excellent source of factual knowledge. It is not particularly designed to be of help to the clinician, but rather the research workers to whom it should be of special value.

NEW EDITIONS

Treatment in General Practice. By HARRY BECKMAN, M.D. Fifth Edition. Pp. xiii+1015. London: W. B. Saunders Company Ltd. 1945. Price 50s. net.

The author points out that the prodigious upheaval of the past few years has deeply affected the science and art of medicine, old concepts have fallen, new ones have arisen and in some cases have fallen too. He has attempted to keep abreast of these numerous developments, has evaluated them and has presented them in a form which would be immediately usable by the practising doctor. The information covers the whole range of medical practice and is very complete. We can recommend this work as an up-to-date book of reference.

Physical Diagnosis. By RALPH MAJOR, M.D. Third Edition. Pp. xv+444, with 437 illustrations. London : W. B. Saunders Company Ltd. 1945. Price 25s. net.

In these days of scientific medicine it is well to remember physical examination of the patient must still play an important rôle in diagnosis. So-called modern methods for the most part are merely supplementary to the careful personal examination of the patient, which is the first duty of the attendant.

Professor Major's book deals with the subject very thoroughly. It is clearly written, well illustrated and beautifully produced. The book is one we can recommend with confidence.

Surgical Nursing and After Treatment. By H. C. RUTHERFORD DARLING, M.D., M.S., F.R.C.S. Ninth Edition. Pp. x+696, with 211 illustrations. London : J. & A. Churchill Ltd. 1946. Price 12s. 6d.

While noting that surgical nursing is best learnt by actual experience in a well-equipped and up-to-date general hospital, the author points out that there is generally little time to have the multitudinous details of surgical nursing explained in the wards. In this book, therefore, he attempts to supply the requisite elucidation. The text embraces a wonderful amount of useful information and the book should be of the greatest value to those for whom it is intended.

Applied Physiology. By SAMSON WRIGHT, M.D., F.R.C.P. Eighth Edition. Pp. xxx+944, with 513 illustrations. London : Geoffrey Cumberlege, Oxford University Press. 1945. Price 30s.

Great advances have been made in Physiology in recent years, and the labour required to compress new information of importance into a reasonably small compass must have been prodigious. It is not possible to detail the variety of new matter which has been added in this edition. An outstanding feature is an increase in the number of illustrations and, to help readers to make an adequate use of them, an appendix has been added in which two figures are carefully described and analysed.

The value of the work lies in the understanding it gives of the mechanism of illness, and no thoughtful clinician will wish to be without it.

Recent Advances in Neurology and Neuropsychiatry. By W. RUSSELL BRAIN, D.M., F.R.C.P., and E. B. STRAUSS, D.M., F.R.C.P. Fifth Edition. Pp. xiv+363, with 32 illustrations. London : J. & A. Churchill. 1945. Price 18s.

Extensive re-writing has been necessary owing to the great progress which has been made by neurology and neuropsychiatry during the last four years. New topics include electric convulsant therapy for mental disorders, prefrontal leucotomy, peripheral nerve injuries, vaso-neuropathy after chilling, neuritis of the shoulder girdle and two newly recognised forms of acute encephalitis. The growth in importance of electro-encephalology as a diagnostic method is emphasised, and its application to neurophysiology, sleep, epilepsy, the psychopathics and the psychoses is described.

The book is well written, easy to read, and the authors are to be congratulated on their achievement.

The Principles and Practice of Rectal Surgery. By WILLIAM B. GABRIEL. Third Edition. Pp. 432, with 248 illustrations. London : H. K. Lewis & Co. Ltd. 1945.

The third edition of this excellent textbook will enhance its already high reputation. Many new illustrations have been added and the book has been brought up-to-date in every respect. It is interesting to note that, in the treatment of prolapse of the rectum in adults, the author has given up the treatment by peri-rectal injections and

has reverted to the severe operations of amputation and the method of Moschowitz. On p. 21 and p. 300 the statement is made that it is unusual for a carcinoma of the anal canal to infect the superficial inguinal lymph nodes until the skin margin of the anus has been reached. There is no anatomical reason why this should be so and it seems a dangerous attitude to adopt. The reviewer has recently seen a case in which a carcinoma at the ano-rectal junction of the mucoid or colloid type caused severe infection of the inguinal nodes on both sides. Otherwise, there is little to criticise in this book and there is no doubt that it is the best textbook on the surgery of the rectum published in this country.

Kettle's Pathology of Tumours. Revised by W. G. BARNARD, F.R.C.P., and A. H. T. ROBB-SMITH, M.A. Oxon., M.D. Lond. Third Edition. Pp. viii+318, with 191 illustrations. London: H. K. Lewis & Co. Ltd. 1945. Price 21s. net.

The lapse of twenty years since the appearance of the second edition of this well-known volume has naturally necessitated considerable revision of the text. Part One, on the general biology of tumours, has been brought up to date by Professor Barnard, while both authors share the responsibility for Parts Two and Three, on the general and special pathology of tumours respectively. Part Two now contains sections on tumours of the nervous tissue, central nervous system, sympathetic system, nervous sheaths and peripheral nerves. New material has been entered under the experimental induction of tumours and other subjects which receive modernisation include reticulosarcoma, neoplasms of bronchus and ovary and Paget's disease of the nipple. The authors have succeeded in giving renewed life and value to an already deservedly popular presentation of the subject.

Psychological Medicine. By DESMOND. CURRAN, F.R.C.P., D.P.M., and ERIC GUTHMANN, M.D., M.R.C.P. Second Edition. Pp. viii+246, with 20 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 10s. 6d. net.

This short introduction to psychiatry has met with considerable popularity. It can be recommended as giving a bird's-eye sketch of modern psychiatric work, and for the most part is a safe guide to undergraduates and to medical officers in the Forces; there is an interesting appendix on War-time Psychiatry. It is somewhat surprising to learn that " Paranoia is now regarded as a still milder form of paranoid schizophrenia." It is hoped that in a future edition that statement will either be eliminated or justified.

Principles of Human Physiology. By E. H. STARLING. Ninth Edition, edited by C. LOVATT EVANS, D.SC., F.R.C.P., F.R.S., LL.D. Pp. x+1155, with 668 illustrations. London: J. & A. Churchill. 1945. Price 36s.

Without increasing its bulk, Professor Lovatt Evans has incorporated in this edition a great deal of the new material which has arisen, or assumed new importance, in the four years since the last publication. This has been achieved by the use of slightly smaller type and by extensive re-writing, for in addition to the recent advances which are discussed room has been found for historical notes on appropriate sections. Nineteen new diagrams have been included; if any adverse criticism can be made, it is that many of the older diagrams might with advantage be revised and replaced. References to reviews and original papers are inserted at the foot of each page.

This book can be regarded as the standard British work of reference on the scientific aspects of Physiology.

Illustrations of Regional Anatomy. By E. B. JAMIESON, M.D. Sixth Edition. Pp. xii+336. Edinburgh: E. & A. Livingstone Ltd. 1945. Price 75s. net.

In his preface Dr Jamieson tells us that the idea of producing this work grew out of a demand by his students for some means of perpetuating the blackboard

diagrams which illustrated his demonstrations. The earlier editions were entirely in black and white but with the appearance of new issues colours have been added until now some of the plates introduce no fewer than seven. The present edition is a work of art and a fine example of British workmanship. It is now available in two forms, a bound volume as well as the seven separate sections with detachable leaves.

Recent Advances in Obstetrics and Gynæcology. By ALECK W. BOURNE and LESLIE H. WILLIAMS. Sixth Edition. Pp. x+357, with 77 illustrations. London : J. & A. Churchill Ltd. 1945. Price 18s.

A new edition of this " Recent Advances " is always received with pleasurable anticipation because of the flare the authors have of making a lively and critical presentation of the essence of the subjects reviewed, be they the results of the application of current opinion and practice or the assessment of trends of thought. This edition comes up to expectation. New chapters have been written on subjects of special topical interest such as " Nutrition in Pregnancy," " Vitamin K," " Still-birth and Neonatal Death " and " Erythroblastosis," while Dr Wilfred Shaw has contributed one on " Ovarian Tumours " and Dr Levitt one on " X-ray Therapy in Gynæcology." This latter is in addition to Dr Rohan William's revised chapters on " Radiological Diagnosis in Obstetrics and Gynæcology." Not only does the book collect together information, but presents it duly correlated, summarised and appraised in such a way as to stimulate thought and questioning.

A Handbook on Diseases of Children. By BRUCE WILLIAMSON, M.D., F.R.C.P. Fourth Edition. Pp. xii+388, with 81 illustrations. Edinburgh : E. & S. Livingstone Ltd. 1945. Price 12s. 6d. net.

The fourth edition of this popular handbook on diseases of children will be welcomed after an unavoidable delay of more than a year during which the book has been out of print. The text has been thoroughly revised. It has also been slightly enlarged and eleven more illustrations have been introduced. Such a comprehensive and concise presentation of the subject in handy form is likely to attract an increasing number of general practitioners and undergraduates.

BOOKS RECEIVED

BARACH, ALVAN L., M.D. Principles and Practices of Inhalational Therapy.
(Blackwell Scientific Publications Ltd., Oxford) 25s. net.

BLACKER, C. P., M.A., M.D., F.R.C.P., and Sir WILSON JAMESON, K.C.B., M.A., M.D., LL.D., F.R.C.P. Neurosis and the Mental Health Services.
(Oxford University Press, London) 21s. net.

Edited by CHRISTOPHER, FREDERICK, B.S., M.D., F.A.C.S. A Textbook of Surgery. Fourth Edition, Revised and Reset.
(W. B. Saunders Co., London) 50s. net.

GOLDEN, ROSS, M.D. Radiologic Examination of the Small Intestine.
(J. B. Lippincott Co., London) 36s. net.

HERNDON, RICHARD F., M.D., F.A.C.P. An Introduction to Essential Hypertension   .   .   *(Charles C. Thomas, Publishers, Springfield, Illinois)* —

KING, E. J., M.A., PH.D. Micro-Analysis in Medical Biochemistry.
(J. & A. Churchill Ltd., London) 10s. 6d. net.

MICHAELIS, L. S., M.D. Anatomical Atlas of Orthopædic Operations.
(William Heinemann (Medical Books) Ltd.) 25s. net.

ROGERS, Sir LEONARD, K.C.S.I., C.I.E., M.D., F.R.C.P., F.R.C.S., F.R.S., I.M.S., and ERNEST MUIR, C.I.E., M.D., F.R.C.S. Leprosy. Third Edition.
(John Wright & Sons Ltd., Bristol) 25s.

THE HEALTH AND WELFARE OF THE
MERCHANT SEAMAN *

By J. A. NIXON, C.M.G., M.D., F.R.C.P.

THE MERCHANT NAVY is the key industry of Britain, yet the number of men employed is comparatively small. In 1942 the number of British merchant seamen was estimated at 120,000, and with the addition of about 45,000 Indians or Lascars and a few thousand Chinese and Arabs, a total of 200,000 might be reached. " Nevertheless " (to quote the *British Journal of Industrial Medicine*), " the hazards in this industry are great ; the risk of collision, of grounding on rocky coasts in heavy seas, fire and explosion. . . . The mortality rates of merchant seamen between the ages of 20 and 64 are approximately double the standard rate for the same age group, the death rate from tuberculosis among seamen being four times greater than among the general population. It has also been shown that 17 per cent. of all deaths occurring within a year of leaving the sea are due to tuberculosis."

Yet the health of merchant seamen is a subject that has never aroused much interest ; extraordinarily few books have been devoted to it, as may be proved by searching the Index Catalogue of the Surgeon-General's Office in Washington, and the Index-Medicus, or in a smaller way, any of the large medical libraries in the United Kingdom. No wonder that Mr Hector Hughes, K.C., M.P., at the Annual Conference of the National Union of Seamen in 1945 described merchant seamen as the " Cinderellas of the Services, serving everybody but themselves and neglecting their own interests."

Before the time of Columbus and Cabot sea travel had consisted in coasting voyages, so that the diseases of the sea were scarcely different from those on land. The problems of health and sickness at sea began with long voyages of discovery. In this respect the Merchant Navy ranks in front of the Royal Navy. In the earliest coasting voyages calls at various ports prevented shortage of food or dietary deficiencies. Shipwrecks occurred and the effects of

* The 1945 Alexander Black Lecture given in the Royal College of Physicians, Edinburgh.

exposure, hunger and thirst were known from the earliest times, but so far as I know no medical records exist prior to the fifteenth or sixteenth centuries. Ships were small and passengers were not numerous. The average complement of passengers was about seventy. Della Valle (*circa* 1612) mentioned that one ship on which he travelled from Constantinople to Cairo carried two thousand. Up to the end of the sixteenth century special galleys sailed from Venice to Jaffa for pilgrim traffic in the summer. The captains of these pilgrim galleys undertook to carry a barber-surgeon and a physician, and to avoid unhealthy ports. Even so the journey had its evils. One pilgrim related " that all sorts of discomforts are met with, suffering greatly from the heat in summer and much troubled by vermin. Huge rats came running over our faces at night. Those near us who fell ill mostly died. The meals were not exactly inviting, the meat had been hanging in the sun, the bread hard as a stone with many weevils in it, the water at times stank, the wine warm, or hot enough for the steam to rise, with a beastly taste to it. Bugs, etc. crept about over everything." The risk of plague breaking out on these Mediterranean voyages was great. For instance, plague carried off at least 500,000 persons in the single city of Grand Cairo in the year 1580.

When long voyages came into vogue the need for ship surgeons was quickly realised. Although in Sebastian Cabot's ordinances for the intended voyages to Cathay in 1553 no mention is made of surgeons, we know from a note found in one of the two ships (the *Bona Esperanza*) which wintered in Lappia, that surgeons were carried. Sir Hugh Willoughby and all his Company were frozen to death on this voyage to Cathay under the patronage of Sebastian Cabot. In the list of " Mariners and Officers according to the Customs and Use of the Seas " taken in the *Bona Esperanza* the names of two surgeons appear, Alexander Gardiner and Richard Molton, taken on at Harwich.

In the " Instructions given by the Lords of the Counsell " to M. Edward Fenton for his voyage to the East Indies and Cathay in charge of three ships he was directed to furnish 200 able persons including the gentlemen and their men, the ministers, chirurgians, factors, etc. When Thomas Candlish sailed from Plymouth into the South Seas in 1586 surgeons accompanied the expedition.

On another expedition about this time, that of the *Delight of Bristol* to the Strait of Magellan, some of the ship's company sent to the Master of the *Robert Burnet* complaining of their sufferings. They charged their Captain, Matthew Hawlse, with starving them and neglecting their health. Among other things lacking they mention " in particular the want of a skilful surgeon." They alleged that Captain Hawlse and the mate, Street, have not only immoderately spent the Companies' provision in butter, cheese, aqua vitae, etc., but have also consumed the sweet meates that were layed up in the ship for the relief of sick persons—which indicates that " medical comforts " were carried. In the account of the last voyage of

Sir Francis Drake and Sir John Hawkins in which they both died, mention is made of the death of James Wood, " Chief Chirurgion of the Fleet," an office which suggests an advanced degree of medical organisation on these expeditions. The length of the voyages not only brought old diseases into prominence, small-pox, plague, dysentery and scurvy, but new ones such as yellow fever, syphilis, and in some measure, malaria, were encountered. Although ague was familiar in Britain the varieties met with in the New World were not recognised as the same disease, and it was called " Calenture " in its new and more malignant forms.

For some curious reason sea scurvy, one of the most devastating scourges of these long ocean voyages, was held to be a different disease from land scurvy.

In parenthesis it is amazing to find how early the cure and prevention of scurvy were established. Dutch sailors as described by Ronsseus had made the discovery that oranges and lemons could be relied upon. From the Dutch, Sir James Lancaster, that greatest of all British shipmasters, learnt how to keep his crews free from scurvy. He persuaded the Hon. East India Company as early as 1601 to issue lemon juice as a routine article of victualling on the Company's ships trading to the East. John Woodall, the first Surgeon-General to the East India Company, in his book *The Surgeon's Mate*, published in 1617, gives to lemon juice the first place amongst all remedies for scurvy. It is strange that Captain Cook, who fumbled with a multitude of remedies, is popularly credited with having discovered how to prevent and cure scurvy. He never appreciated the experience of Lancaster nor the insistence of Woodall upon the superiority of oranges and lemons.

During the early years of the eighteenth century voyages of discovery and privateering under letters of Marque went on apace. Men like Dampier and Woodes-Rogers were in great demand as leaders of these expeditions. One of the best known was that of the *Duke* and *Dutchess* from Bristol under Woodes-Rogers' command, with Dampier as one of the navigators, when Alexander Selkirk of Largo was brought back from Juan Fernandez. Dr Thomas Dover (famed for his powder) took part as representative of the owners and Chief Medical Officer with at least three other surgeons and two assistants. Woodes-Rogers's voyage has always stood in the annals of health at sea for the remarkable freedom from sickness. During the greater part of the eighteenth century Britain was engaged in European wars to such an extent that voyages of discovery gave place to naval activities. Passenger travel and trading voyages were largely suspended, with the exception of travel round the Cape of Good Hope to India. Even the East Indiamen were nearly as much ships of war as ships of commerce. At the later part of the eighteenth century and during the early years of the nineteenth, however, especially after the close of the Napoleonic Wars, new countries were being opened up, settlers,

officials and troops were all making their way to distant lands, trade and traffic on the high seas increased, including the slave trade. The Merchant Navy rapidly developed, yet sanitary science and preventive medicine lagged hopelessly behind. Accommodation on ship-board was insanitary in the extreme. Larger ships were built, but the additional space was designed for freight. The provision made for passengers was a secondary consideration, whilst the quarters of the crew ranked last of all and were wretched. It was a lucky ship that cleared from a British port without some contagious disease amongst the passengers or crew.

The accommodation and life on board ship were, except in fair weather, miserably foul and well-calculated to produce sickness of all kinds. Ventilation in bad weather was hard to secure, the bilge water could scarcely avoid contamination, and it became horribly smelly. Victuals grew weevily, decayed and stank; drinking water, if it did not run short, became well-nigh undrinkable. Yet canned food was supplied to Napoleon's armies. The East India Company took the lead in endeavouring to prevent sickness and preserve health at sea. Lemon juice was shipped in casks so that it remained effective against scurvy and drinkable during the longest sea-voyages.

Towards the end of the eighteenth century the East India Company began to have their surgeons examined by the Surgeons' Company of London, although the examination was of a very elementary nature. In 1798 the Company agreed to recognise the diploma of the Edinburgh College of Surgeons without further examination in London, although the Navy and Army refused to do the same. As early as 1629 the Charter granted by Charles I to the Barber Surgeons of London instructed them to examine the Sea Surgeons and " enacted that no one should go out from the port of London or send out any apprentice. servant or other person from the same port, to act as Surgeon to any ship whether in the service of the Crown or of a Merchant, unless they, their instruments and their chests had first been examined and allowed by two of the Governors of the Mystery." This does not, as has been represented, compel every ship sailing out of the port of London to carry a surgeon. It requires any surgeon sailing on any London ship to be examined, together with his instruments and drugs, by Governors of the Barber Surgeons Company.

Sir Francis Drake seems to have been the first English sea-captain to show special consideration for the seamen in his ships. A. E. W. Mason, in his life of Drake, says, " Hitherto the mariner on a Tudor ship was a creature of the meanest reckoning. On a ship of the Navy the soldier was all in all; on a trading ship, if a third of the crew which set out was alive to bring her home everyone was well content." The mariner was the sea's beast of burden. Drake in his earlier voyages had brought in a rule that the gentlemen must share in the work of the sailors and in his voyage of 1577 he announced publicly, " I must have the gentlemen hale and draw with the mariner and

the mariner with the gentlemen." Mason describes this as the first charter for the mariner and the introduction of a new era at sea. But there was no law making it compulsory to carry a surgeon in any merchant ship until the reign of George III. It is true that the East India Company carried surgeons on their ships—they did so of their own accord and perhaps because they found it worth while. In the twenty-sixth year of George III's reign, Arctic whalers were compelled, under an Act of Parliament (26 Geo. III, *c.* 41) regulating the Greenland Fisheries, to carry a surgeon. A few years later, in 1789, it was enacted that no slave ship should sail unless there was at least one surgeon on board who must produce a certificate of having passed his examination at Surgeons Hall (London), or at some Publick or County Hospital, or at the Royal College of Physicians or Royal College of Surgeons in Edinburgh.

The first separate Act for regulating passenger ships was 43 Geo. III, *c.* 56. By this act every vessel carrying fifty persons was required to carry a surgeon possessing a certificate of having passed his examination at Surgeons Hall, London, or at the Royal College of Surgeons of Edinburgh or Dublin. These enactments did not all prove equally beneficial to the seamen. On the whalers it was to the advantage of the owners to keep the crew in good health because the harvest of the Arctic Seas must needs be gathered by the crew. The log books of the two Scoresby's, father and son, show that on the whole, sickness was relatively mild. William Scoresby, junior, published his account of the Northern Whale Fishery in 1820.

On the slave ships there was a different story. It was greatly to the advantage of the shipowners if the crew deserted on reaching America. The deserters forfeited their wages for the outward journey, the owners only had to pay the new crew for the homeward journey. The Report of the Committee of Enquiry shows how the crews of slave ships fared. Surgeons were carried to attend to the health of the slaves only; they had no responsibility for the officers and crew. Many of the witnesses gave evidence of the way the crews were treated. In one instance a surgeon refused to attend to an injured officer saying that he was only entitled to be treated by the Captain. One seaman testified that he was cruelly beaten both by the Captain and the Surgeon, that he was half starved and that the surgeon neglected the sick seamen, alleging that he was only paid for attending the slaves. Overwhelming corroboration of these stories was given by Falconbridge, a Bristol student, who sailed four voyages as surgeon on slave-ships. Lettsom has recorded his opinion that Falconbridge's evidence was the principal cause of the Bill for abolition of the slave-trade being brought in and passed. When one reads the evidence one is inclined to think that the treatment of the crews was a factor of scarcely less importance than the plight of the enslaved negroes in bringing about the suppression of the trade.

At the close of the eighteenth century the colonisation of New

South Wales began with the arrival at Sydney on 26th January 1788 of what is known as the First Fleet consisting of eleven vessels carrying about 1000 persons. On these convict ships the Government made careful provision for the convicts. Sanitation was well looked after, whilst exercise, education, religious instruction, clothing and diet were prescribed by regulation. An excellent account of these voyages was written by C. A. Browning, M.D., Surgeon R.N. and published in 1846. Exception had been taken to the ample scale of living allowed to these exiles from their country for their country's good. " If the objectors to an adequate scale of rations," he wrote, " desire the death of the convict, that can surely be secured without the professional attendance of a medical officer by means far less expensive to the country than the usual provision for a long voyage." Here again we see that the cargo, whether slaves, convicts or later on, of fare-paying passengers, were the objects of the owners' solicitude, not the crews, with the exception of the " whalers." In the latter ships the sailors not only navigated the ships but they secured the paying cargo.

When at the beginning of the nineteenth century steam came to replace sail, there was little or no improvement in the living conditions of the crew. Voyages were shortened but this only reduced the liability to scurvy. Engines with their boilers, machinery and screw-shafts or paddleshafting, and the necessary adjunct of coal bunkers usurped some of the central space of the hull. All other available space was claimed either for cargo or passengers and the crews were crowded into the forecastle. The quarters were more wretched than ever. Ventilation was worse in steamers than in sailing ships. Rations, although with advancing knowledge these might have been improved, remained no better than in previous times. Drinking water alone seemed to be capable of better storage and in the course of time distillation became practicable at sea.

The increasing speed made possible by steam increased the number of collisions with ships and with ice ; and collisions when they occurred had more serious consequences. New injuries occurred from machinery, engine-room explosions and stoke-hold burns. The story of the expansion of our Merchant Navy is a pitiful story of exploitation. Neglect, criminal neglect and deliberate sailing of unseaworthy vessels are crimes with which ship owners have been charged, and the charges are unrefuted.

In the nineteenth century the rankness of the owners' offences brought forth a champion of the mariners' cause in the House of Commons. Samuel Plimsoll was born in Bristol in 1824. At the age of 27 he was appointed Hon. Secretary for the Great Exhibition in Hyde Park. In 1868 he was elected M.P. for Derby, and in 1870 he opened his campaign against unnecessary loss of life and property at sea. In 1872 he published a small book, *Our Seamen*, which deals with unseaworthy ships and loading. This book was the first publicly to

accuse owners of sending " coffin ships " to sea, heavily insured in the hope and expectation that ships and crews would never be heard of again and the owners would draw the insurance money, more valuable by far than the ships and their cargoes.   Any officer or seaman who, after signing on failed to join his ship, was liable to prosecution.   Punishment in those times was savagely heavy and the allegation that a man feared to sail because the ship was suspected of being unseaworthy seems, from the court reports, to have merely enraged the Magistrates who increased their sentences.   Even now it makes one's blood boil to read of the conspiracy that seemed to exist between shipowners, magistrates and parliament, to stifle any leakage of the truth as the crews knew it.   In 1873 there was a Royal Commission on shipping, with the 12th Duke of Somerset, who had been First Lord of the Admiralty, for Chairman.   From the recommendations of this Commission, which, owing to the firmness of the Chairman, probed fairly deeply into shortcomings and worse, a Merchant Shipping Bill was brought into the House of Commons. On 22nd July 1875 there was a scene in the House in which Plimsoll played the leading part.   He spoke of shipowners, members of the House of Commons, who sent sailors to their death, and said he would " unmask the villains."   This caused an uproar, and the Speaker held that Plimsoll had been guilty of an unparliamentary expression. Disraeli, the Prime Minister, joined in the condemnation of Plimsoll whose suspension from the House was moved and carried.   Plimsoll was overcome by an apparently hysterical and speechless rage, and was with difficulty induced by his friends to bow to the Speaker's ruling.   The *Times* on the following day (23rd July 1875) came out with surprising vigour in support of Plimsoll.   It condemned Disraeli and his Government in unmistakable terms and pointed out, with satisfaction, that although Plimsoll had apologised and withdrawn every term or expression which transgressed Parliamentary usage, he did not withdraw any statement of fact.   If one turns up the Reports of Parliament one finds that Plimsoll named one member (Mr Bates) who had sent unseaworthy ships to sea, that the ships had been lost and the insurances drawn.   The member defended himself lamely, but had to admit the correctness of Plimsoll's facts.   After the scene and the admissions the Merchant Shipping Act of 1876 was passed and became law.

A short survey of books dealing with sea diseases will not be out of place.

First among British authors must be placed Woodall, who in 1617 published *The Surgeon's Mate*.   In this book the value of oranges and lemons in preventing and curing scurvy is authoritatively laid down.   He was Surgeon-General to the East India Company, and why the practice of this Company was not adopted by the Navy for 200 years has not up to now been explained. Oranges and lemons or their juices were official articles of victualling on East Indiamen, and ships' captains wrote letters of complaint to the directors

when, as sometimes happened, they found their ships unprovided with these anti-scorbutics.

During the eighteenth century many books were published, describing the commoner sea diseases. Lind, Blane and Trotter are perhaps the most famous. Lind, an M.D. of Edinburgh and a Fellow of the Royal College of Physicians of Edinburgh, spent nine years at sea, 1739-48. In 1754 he published a *Treatise on Scurvy* and in 1757 *An Essay on the most Effectual Means of Preserving the Health of Seamen in the Navy*, and another in 1768 on Tropical Diseases. He was a man of ability and originality, with moreover, a personality that won the confidence of the naval authorities, who appointed him Physician to Haslar Hospital and grudgingly adopted a few of his suggested reforms. Lind claimed that he was one of the first to suggest the distillation of fresh water from sea water by solar rays. Trotter called him " The Father of Nautical Medicine."

Sir Gilbert Blane was a fine administrator and by the weight of his personality brought about many improvements in the Navy, but he made no outstanding original observations on disease and its prevention. He is one of the few writers who mentions night-blindness as being sometimes associated with scurvy, and he is very forthright, more so than Lind, about the prevention and cure of scurvy. " There is nothing known," he wrote, " except lemon juice, which possesses any certain and considerable curative power over this disease without the assistance of proper diet." It is surprising that he seems to have been unacquainted with the virtue of oranges, upon which the Dutch as well as Lancaster, Woodall and Lind, had laid stress. Blane, in addition to the usual list of diseases which occur on sea voyages, gives the common casualties that are met with on board ship :—

1. Drowning.
2. Suffocation from foul air in the hold.
3. Poisons, including bites (snakes and venomous insects) and poisoned weapons.
4. Frost bite.
5. Burns.
6. Wounds and lock-jaw.

His reputation, however, rests securely upon his having succeeded in persuading the Navy Authorities that lemon juice should be supplied to the British Navy for the prevention of scurvy, so that at last, in 1795, the issue of lemon juice to ships of the Navy was ordered by the Admiralty, just two hundred years after its adoption by the East India Company. Blane's entrance into the Navy was unusual. Dr William Hunter recommended him to Lord Rodney with whom he sailed as private physician, but without any public appointment. Rodney soon made him physician to the Fleet. He performed the duties of that office so ably that on the unanimous application to the Admiralty of all the principal officers who had been on the Station he was rewarded with a pension from the Crown. He obtained the M.D. at Glasgow in 1778, although an Edinburgh student, settled in London in 1781 and was ultimately appointed by Lord Spencer to be one of the Commissioners of the Sick and Hurt.

Thomas Trotter is in my opinion the greatest of our British writers on disease at sea. He was baptised at Melrose on 3rd August 1760, son of John Trotter and his wife, Alison Marr, and studied medicine at Edinburgh

University.   He entered the Navy as a Surgeon's Mate at 18 and had a truly varied experience at sea, for when in 1783 the war ended, he was unemployed and sailed as surgeon on a slave ship, being thoroughly disgusted with his experience.   On another occasion finding himself on half pay, he sailed on an East Indiaman.   In 1784 he resumed his studies in Edinburgh; in 1786 published his *Observations on Scurvy*, and in 1788 obtained his M.D. by thesis, " De ebrietate, ejusque effectibus in corpus humanum," a translation of which he published, in 1804, as *An Essay, Medical, Philosophical and Chemical, on Drunkenness, and its Effects on the Human Body*.

Trotter was a man of accurate powers of observation, not too respectful of the opinions of the medical authorities of his time and capable (as his reports show) of vigorous and independent expression.   James Anthony Gardner who sailed with him in *H.M.S. Edgar*, 1787-89, described him as " a most excellent fellow with first rate abilities, an able writer and a poet." He published in 1797 *Medicina Nautica : an Essay on the Diseases of Seamen*.   His book (in 3 volumes) is full of his own observations, one of the shrewdest being that communication with the shore produced yellow fever. He relates that Vice-Admiral C. Thompson, who lately commanded in the West Indies was so certified that the disease uniformly disappeared from ships as they increased their distance from the shore, that he sometimes insisted upon ships putting to sea when their condition otherwise was unfavourable. Trotter comments that an imitation of this practice will always be attended by salutary consequences.   Blane put the distance that yellow fever contagion could travel as two cable lengths in Jamaica.

Of recent years few books have been published dealing with disease in the Merchant Navy.   W. E. Home took a good deal of pains on this subject, however, about 1920.   His little book, *Merchant Seamen, their Diseases and their Welfare Needs*, published in 1922, may almost rank as a classic. It is possible from the Board of Trade returns to find out something as to deaths and death rates amongst merchant seamen, but almost nothing about sickness incidence nor invaliding.   From Home's book the death rates per 1000 are compared with those of the Navy and Army.

The incidence of disease in the Merchant Navy is high.   In some diseases, notably pulmonary tuberculosis, much higher than amongst the civilian population and much higher than in the Navy at present.   Sheldon Dudley has reminded us that pulmonary tuberculosis has always been an occupational disease of seamen, owing to the confined spaces in which they must live at sea.   Nelson, in a letter to Dr Baird (22nd September 1804), wrote, " Experience teaches us that this climate (of Toulon) is the worst in the world for hectic complaints, at least it is so at sea.   Of the few men we have lost, nine in ten died of consumption."   Dudley puts the sickness rate in the Mediterranean Fleet between 1830 and 1863 at about 8 per 1000 from pulmonary tuberculosis.   In the years 1901-5 the figure was 3·9 per 1000. The death rate had fallen from 2 per 1000 to 0·53 per 1000.   Home showed it in 1913-14 as 0·27 per 1000 in the Royal Navy.

In 1913-14 Enteric Fever caused a death rate of 0·22 per 1000 in the Merchant Navy against 0·24 in the Royal Navy and 0·10 in the Army. Pneumonia 0·26 in Merchant Navy, 0·30 in Royal Navy, 0·21 in Army. Alcohol 0·69 in Merchant Navy, 0·03 in Royal Navy, and 0·01 in Army. (Here I suspect the Masters were more ready than the Medical Officers of the services to certify " alcohol ").

Circulatory diseases, 0·44 Merchant Navy, 1·20 Royal Navy, 0·25 Army. (Heart disease accounts for many deaths ashore.)

Diseases of digestive system, 0·32 Merchant Navy, 0·28 Royal Navy, 0·38 Army.

Injuries rank very high, 4·14 per 1000 Merchant Navy, 1·07 Royal Navy, 0·62 Army.

Suicides, 0·30 Merchant Navy, 0·11 Royal Navy, 0·18 Army.

The total death rates from all causes are 7·79 Merchant Navy, 3·25 Royal Navy, 2·992 Army. As Home observes, the ages are different. The Merchant Seamen being the oldest. Tuberculosis and respiratory diseases other than pneumonia do not rank high—probably the men leave the sea and die perhaps many years later. Tuberculosis rate—0·14 Merchant Navy, 0·27 Royal Navy, 0·25 Army.

Home proposed to deal with pulmonary tuberculosis in Merchant Seamen on the lines of silicosis in other industries.

Sea diseases as enumerated by Trotter.   1797.

Fevers—Typhus, Ague, Yellow Fever	(Intoxication)
Flux—Dysentery	Scurvy
(Smallpox)	Venereal complaints
Catarrhal complaints	Ulcers
(Rheumatism)	Bruises, etc.

as given by Blane.   1782.

Fevers	Venereal complaints
Fluxes	Pectoral complaints
Accidents—Bruises, cuts, scalds	Colds
Scurvy	Angina
Ulcer	Gravel
Smallpox	Fistula-in-ano
Rheumatism	Fractures

as given by Home.   1913-14.   (From Board of Trade Blue Book.)

Smallpox, Enteric Fever, Pyrexia, Yellow Fever, Malaria	Tuberculosis
Dysentery	Rheumatic Fever
Pneumonia	Other Infectious Diseases
Septic Diseases	Parasitic Disease
Tuberculosis	Alcohol
Venereal Disease	Other Poisons

Other General Diseases

Diseases of Nervous System	Diseases of skin, etc.
Mental Diseases	Debility and unknown
Diseases of circulatory system	Heat Stroke
Diseases of respiratory system	Injuries
Diseases of digestive system	Suicide
Diseases of urinary system	

Whatever verdict history may pass upon the League of Nations the reputation of the International Labour Office is secure. Under the auspices of the I.L.O. a Joint Maritime Commission was organised

in 1920. It consists of a Chairman and two members appointed by the Governing body—seven representatives of the shipowners and seven of the seamen. Shipowners and seamen alike have always attached great importance to the Commission. It has functioned as a Standing Committee for advising the Governing body of the Office on Maritime Labour questions. Its reports are historical documents of prime importance to anyone who wants to study the health and welfare of mariners. One such report was issued after the 13th Session of the Joint Maritime Commission held at Geneva in 1929. This dealt with the Promotion of Seamen's Welfare in Port. The introduction by Havelock Wilson and P. Salvesen is worth noting :—

" The Community's consciousness and responsibility for seamen's conditions of life ashore are under the blunting influence of habitual indifference and particular interests are allowed to play far too large a part. Seamen are especially the victims of unscrupulous attempts to rob them of their money. In many seaports businesses of an inferior character have long been allowed to develop under conditions which no wide-awake community should tolerate. Great numbers of bars, low places of amusement and lodging houses and the like, exist, while trading ashore and on board vessels in port goes on uncontrolled to a far too great extent. Often the lighting and patrolling of dock areas is inadequate. Access to ships in port is far too easy to strangers and persons of bad character. A more or less public street traffic is carried on by loose women, and the activities of keepers of houses of ill fame play no small part in the influences to which weak characters are exposed and by which many are ruined."

Here is what Home had written in 1922 :—

" An ordinary man, besides his working associates, has his wife and home, or his club, or his cronies in the usual public house. He has, on shore after his work, at least a place to sit down. The sailor has none. Where, if he goes ashore in any port he has reached, has he to sit down but in a public house ? And once there, how can he justify his occupying a chair unless he drinks and goes on drinking ? "

Home says as an officer—" It was a great thing to be in a club where one had not always to be doing something for the good of the house to pay for one's chair." Nowadays, there are Merchant Navy Clubs here and there and Sailors' Homes in many ports all the world over. In foreign ports a " Missions to Seamen's " launch and the port Missionary are eagerly looked for. The Missionary often takes the men ashore and runs them back, and he does not get them into mischief.

Home concludes—" If the lonely, helpless man was stinted of leave, bullied and defrauded by his captain and the friends he made ashore, how could he raise himself and improve ? But the 1906 Act did help him."

In the days of the slave-trade it was to the advantage of the owners, as we have seen, for the crew to desert. But this held good throughout the greater part of the nineteenth century. In a Report to the House of Commons arising from a question by Admiral Field, British Consuls in various foreign ports gave their idea of the causes which made

desertion so prevalent (14,000 a year).   The Consul-General at Valparaiso, Sir B. Cusack-Smith, asserted that it was a regular practice for some masters so to harass, irritate and abuse their seamen, that these desert.   The master then avoided paying their wages.   The Vice-Consul, Mr Rhind, at Rio de Janeiro, mentioned as the first cause of desertion " a desire on the part of ship-masters to get rid of their crews in order to profit by the confiscation of their wages."

Some masters did more than irritate their seamen into deserting —they had an arrangement with boarding-house keepers ashore to detain men by drink, drugs or actual violence, so that when the ship sailed the men did not join the ship and were dealt with as deserters. The system of profits was more complicated than the mere pocketing of wages.   The boarding-house keeper undertook to supply substitutes (who might be Shanghai-ed on board), receiving so much per head, charged of course to the owners, for his trouble.   The " Crimp " or boarding-house keeper paid the master so much per head for every seaman he engaged in this fashion.

The Act of 1906 stopped the confiscation of these wages. Money due to deserters or seamen who, from illness or other causes, do not complete the voyage must now be handed, with an account, to the Board of Trade.   There is a loophole here, however, over deserters in Home Ports.   Money due to such deserters need not be handed over to the Board of Trade.   A foreign going ship arrives for two ports, first Liverpool, then Bristol, for instance.   If the man deserts at Liverpool or is left behind there, the wages he should have received at Bristol are not handed to the Board of Trade but go into the owner's pocket.

I have been given a copy of the International Seafarers' Charter —a programme of post-war conditions adopted at an Internal Sea-farers' Conference in July 1944.   This is now being discussed at an I.L.O. Congress in Copenhagen.   Many of the suggestions were discussed at an I.L.O. Conference in 1929 and a questionnaire on the subjects was sent to each Government participating.

The British Government, whilst agreeing with almost all the proposals, considered that legislation could only proceed on a National, not an International basis.   One excellent decision in 1929 was the promotion of seamen's welfare in port, a crying need.

The parts of the Charter dealing with Health and Safety are numerous, and include : Hours of manning and time off ashore, Catering, Food, Cooking and Messroom stewards, Accommodation, Hygiene and Medical Services.   In order to form an idea of what is not supplied, paragraphs 96 to 125 should be read in their entirety :—

Accommodation, Hygiene and Medical Services

96. Far too little attention has been given to the accommodation of ships' crews, although admittedly progress has been made in this direction recently. The poor quality of crews' quarters has made itself doubly felt in wartime.

There have been numerous conflicts and many changes have had to be made to make things just tolerable. The unhealthy conditions aboard deter many from choosing or continuing a career at sea.

97. It may be expected that modern ideas about accommodation and hygiene will also have their effects in the shipping industry ; that, on the one hand everything will be avoided making for discomfort and uncleanliness, and that on the other it will be borne in mind, in designing and building ships, that seafarers spend a considerable portion of their lives there. For that reason we think it would be desirable if, among other things, seafarers' organisations were consulted in connection with plans for building and converting ships in so far as the character and the situation of crews' quarters are concerned.

98. The following recommended standards, many of which exist already in more advanced countries, are regarded by the seafarers as the minima for all new ships ; they should as far as practicable also be introduced in ships already afloat.

99. All living quarters should as far as practicable be situate amidships.

100. For all officers there should be separate cabins with a floor space of at least 100 square feet.

101. To promote communal feeling on board, as well as to facilitate the work of the catering personnel, there should be one officers' mess.

102. Adjoining the officers' mess there should be a small mess for a few persons where the engineer on watch can have his meals—an arrangement especially convenient during periods when other officers are wearing white uniform.

103. Each department should have a separate office, so that no officer's cabin need to be used as office and reception room when a ship is in port.

104. In all ships over 1200 tons gross the crew should be housed in two-men cabins ; in smaller ships over 400 tons gross, not more than four men should share a cabin. The free floor space should be at least 12 square feet per person.

105. There should be a ventilated full-length locker for every member of the crew. Lockers should be placed in the cabins.

106. Wooden bunks should be entirely eliminated. To counteract vermin, furniture should be of plastics and " non-sweating " metals such as chromium tubing. A reading lamp should be provided over each bunk.

107. Bed and bedding should be supplied by the owners to all officers and men. The beds should be provided with spring and rubber mattresses, which are expensive but very durable. This type of mattress is also vermin-proof and can be used for life-saving purposes, as it will keep a man afloat. Further, each bed should be provided with three blankets, two sheets, pillow, pillow-slip and bed cover. Sheets and pillow-slips should be changed fortnightly.

108. Soap and towels should be provided to all officers and ratings.

109. Owners should be responsible for all laundry expenses of officers and men, including their personal belongings.

110. Crews' quarters should be distinct and apart from messrooms. All ships over 400 tons gross should have messrooms for deck and engine-room personnel, and ships over 3000 tons gross or with a catering personnel of four or more persons, a special mess for the catering personnel. Messrooms should be adjacent to the galley and where possible, with service hatch to

obviate the carrying of food for long distances. All messrooms should be fitted with filtered drinking water syphons.·

111. Eating utensils should be provided by the owners. Plates, cups, etc., should be of china or heat-proof glass.

112. Cabins and messrooms, both of officers and men, should be heated and ventilated through a system of conditioned air. Ventilation should not depend solely on portholes and fans. The porthole should be big enough to allow a man to escape through it.

113. To facilitate cleaning of living quarters, messrooms, etc., and to keep them free from vermin, bulkheads should be covered with plastics and floors with steelite compositions instead of wood. Floors should have rounded-off edges to avoid crevices.

114. Where quarters have to be fumigated, cyanide gas should be used rather than sulphur.

115. Smoke rooms with recreation and library facilities should be provided for both officers and ratings.

116. Ships over 400 tons gross should have washrooms with fixed wash basins, shower baths and bathroom for all departments. Wash basins should be laid on with fresh water. When the steam boiler is on, hot water should be available in washrooms and bathrooms.

117. W.C. accommodation should be separate from washrooms and bathrooms and should be fitted with urinal porcelain stalls. There should be at least one W.C. for every eight men and a minimum of two for officers. W.C. accommodation for radio officers should be situated near their service post. Proper toilet paper should be provided.

118. All ships should have a small laundry with electric washing machine and adjacent drying room, to enable men to do their own laundry and the catering staff that of the ship on long voyages. The drying room also to be used for men to dry their clothes when coming wet from watch.

119. Walls and floors should be tiled in all toilet and laundry accommodation. All bathrooms and toilets, as well as mess and sleeping quarters, should be kept clean by the messman of the department concerned and should be inspected daily by the chief steward or master.

120. Ships with a crew of not less than 13 should have a special sick bay with at least one bed. The sick bay must be well lighted and ventilated, situated amidships, and must not be used for any other purpose.

121. Ships carrying more than 100 persons (passengers and crew) shall have a doctor aboard.

122. Ships not carrying a doctor or surgeon should have one officer who holds a certificate of competency in first aid and who has undergone training in a general hospital.

123. Where possible opportunity should be afforded during the voyage for members of the crew to obtain elementary knowledge of first aid.

124. Medical chests should be kept up to date, inspected and checked on every voyage to ensure that they are complete.

125. Facilities for getting medical advice per radio both from shore and from ship to ship should be improved and free.

Arising out of The International Seafarers' Charter a new Bill has been drafted to amend the legislation governing the lives of merchant seamen, which will shortly come before Parliament.

Mr Hector Hughes, K.C., addressing the Annual Conference of N.U.S. on 24th July 1945 said that progress in the improvement of the conditions had been lamentably slow.   The Bill of 53 sections deals with the question of manning which formerly concerned only the safety of the ship and not the needs of the crew.   Accommodation for crews on many ships is still a disgrace.   In merchant steamers of the U.S.A. each seaman is provided with a separate bunk ; in the Canadian Merchant Service one cabin accommodates three seamen. The excellent quarters on American steamers handed over to British owners have been altered to suit British standards.

Already our Parliament has, by amendments to the Merchant Ships' Act, given effect to the recommendations of the International Convention for the safety of life at sea.   Rules were enacted in 1932 dealing with life-belts and saving appliances, life-boats and their equipment, motor boats, rafts, buoyant apparatus, distress signals, signalling lamp, direction-finding apparatus, load-line, watertight doors, bulkheads, wireless, regulations for collisions, ice, and helm orders.

In 1942, at Montreal, a Memorandum was drawn up at the request of the Joint Maritime Commission which deals with life-saving measures for merchant seamen in time of war.

So progress is being made.   I have tried to trace the measures for protecting the welfare of seamen from the time of Drake up to the present time when the Joint Maritime Commission is in session at Copenhagen.   Soon it may not be possible to say that our Merchant Shipping Acts are less careful of the health of seamen than they are of sea-birds damaged by the discharge of oil from Diesel-engined steamers.

GLASGOW MEDICAL EXHIBITION

AN Exhibition of surgical instruments, apparatus and appliances, recently introduced pharmaceutical specialities and other aids to medical treatment, will be held in the St Andrew's Hall, Glasgow, from 10th to 14th June next.

This Exhibition, in which leading manufacturers from all parts of Scotland and England are represented follows the lines of those which have been organised by the same management annually in London for forty years, and prior to the war, bi-annually in Glasgow.

Admittance to the Exhibition is strictly confined to members of the Medical and Dental professions, and the public will be rigidly excluded.

DYSPHAGIA DUE TO CAUSES OTHER THAN MALIGNANT DISEASE *

By A. S. JOHNSTONE M.D., F.R.C.S.Ed., D.M.R.E.

THE subject I have chosen for this lecture lends itself to radiological study for, indeed, cases of dysphagia are so readily examined that it is difficult to understand why our knowledge of œsophageal lesions has been so backward. Perhaps it was the bogey of the poor operative risk that kept the surgeon's interest below the diaphragm; but, with the remarkable technical advances made in thoracic surgery during the past fifteen years, there is no longer any justification for our neglect.

Dysphagia means difficulty in swallowing, and when an elderly patient begins to suffer from this complaint malignant disease must first be excluded. It may, therefore, seem wrong to omit cancer from this discussion but it is my purpose to bring before you some of the less known conditions which, I believe, owe their recognition in no small measure to advances in radiological diagnosis.

Difficulties in swallowing may arise from disorders of the complicated physiological mechanisms involved; from obstructions within the lumen of the œsophagus; or by pressure effect from without. Before embarking upon a survey of the pathological lesions a brief review of the mechanism of swallowing might be helpful in the appreciation of the abnormal. The initial propulsion of food into the œsophagus is made by the tongue acting in concert with the pharyngeal constrictors after the larynx has been elevated by the hyoid muscles (Fig. 1). The bolus is shot into the œsophagus with considerable force. That food is sucked down by " negative " pressure, a theory advocated by Barclay,[1] appears improbable, for Allison,[2] using the upper segment of an œsophagus brought out on to the chest wall during a reconstruction operation, was able to demonstrate a positive pressure equal to thirty inches of water during the act of swallowing.

The voluntary movement of swallowing promotes in the œsophagus a primary wave of peristalsis which travels down to the cardia. Secondary waves of peristalsis are said to start just above the level of the aortic arch, but these are involuntary and are stimulated locally by the presence of a bolus. The wave extends upwards—which may cause a primary contraction if regurgitation occurs into the pharynx —and downwards in a manner similar to the primary wave.

Physiologists have described other movements such as a tonus contraction, which may last from a few seconds to several minutes, and rapid local contractions of the circular muscle which last less than

two seconds. The latter are called tertiary contractions, and are independent of any voluntary mechanism.

The motor nerve of the œsophagus is the vagus and normal stimulation causes muscle contraction with relaxation of the cardia. The function of the sympathetic nerves is still a matter of doubt but they probably exert a restraining influence and tend to contract the cardia.

So that I may proceed systematically with the pathological conditions I propose to classify them according to the age groups in which they are most commonly found in the radiological department of a busy general hospital. The list, though incomplete, is long enough to make it impossible to deal fully with every lesion so that only a few points, chiefly radiological, will be brought out in each case.

THE FIRST DECADE

Congenital Atresia.—Congenital atresia of the œsophagus is a rare condition but its existence should be suspected when the new-born baby chokes, coughs and goes blue on taking its first and subsequent feeds. The diagnosis, quickly made by finding in the œsophagus a complete obstruction to the passage of a soft rubber catheter, can be confirmed radiologically by instilling a few drops of lipiodol, which reveal the typical cul-de-sac opposite the third thoracic vertebra.

Owing to their close embryological development, fistulæ between the œsophagus and trachea or a main bronchus are common. The lipiodol may outline a communication between the upper œsophagus and the trachea, but the commonest abnormality, amounting to 80 per cent. of cases, is a fistula between the lower œsophageal segment and the trachea, or a main bronchus. Its existence is revealed in the radiograph if the stomach and small bowel are distended with air (Fig. 2). A simple test was described by Allison [3] who found that, in these cases, the saliva gives a strong acid reaction to litmus. Although the interest in this abnormality is generally confined to the museum, it is important to remember that if surgical treatment is ever to be successful (and there are now several recorded cases), it must be undertaken before the onset of bronchopneumonia and inanition; thus, early recognition, within the first twenty-four hours, is imperative.

Congenital Stricture, Web, Shortening and Spasm.—During the first few years other congenital lesions, of a less serious nature, may become manifest. The inarticulate infant, who cannot describe its dysphagia, signifies the difficulties in a practical way by vomiting or regurgitating. This becomes more pronounced when solid food is added to the diet, and it is usually at this stage that the mother seeks advice although she may admit that the baby has always been troublesome with its feeds. Boys are more frequently affected than girls. The vomiting presents certain characteristic features. Although

variable in frequency it always occurs during a meal, sometimes coming on after the first few mouthfuls and then the rest of the feed may be taken without difficulty. At other times it may occur towards the end of the meal. Lumpy food may precipitate an attack, and as the child gets older it learns to chew its food carefully and laboriously. Older children do not feel any nausea before vomiting. Untreated cases suffer from under-nourishment ; under-development may follow.

On fluoroscopy a number of lesions may be demonstrated although the exact pathological cause is not often recognised. Using thick barium a stenosis may be found in the œsophagus opposite the seventh thoracic vertebra or lower down at the cardia. Findlay considers the stenosis to be a simple narrowing, without wall changes, due to a developmental defect ; but he points out that other lesions, such as a fibrous web, a fibro-muscular thickening or a localised spasm due to an inflammatory lesion lying adjacent, may produce exactly the same picture and be indistinguishable one from the other. A congenital shortening of the œsophagus due to incomplete development of the lower segment is not uncommonly found, and the herniated gastric pouch is demonstrated when sufficient barium has entered the stomach. Sometimes the vomitus contains fresh or altered blood due to the onset of œsophagitis in the stenosed portion.

Many of these cases respond to gentle dilatation with a soft rubber catheter but some require more vigorous stretching with bougies. The stenosis may occasionally become so complete that a temporary gastrostomy or jejunostomy is required. The opinion has been expressed that if left alone the children will grow out of their disability. While this may be true in cases with a strong nervous or hysterical background it cannot be recommended as a principle of treatment.

THE SECOND DECADE

Congenital Stenosis. Simple Stricture.— The child with a neglected stenosis develops into an undersized adolescent with the reputation of possessing a small swallow. As long as he is judicious in his diet he suffers no inconvenience, but a hidden fruit stone or similar object may precipitate a sudden obstruction. The radiological diagnosis in many of these cases is straightforward with the sharply-defined narrow stricture, the smooth margins, and sometimes a shortening of the lower segment with the gastric mucosa drawn up through the hiatus (Fig. 3).

The impaction of a foreign body stimulates vigorous secondary waves of peristalsis, which can produce a sensation of pain usually felt behind the manubrium sterni. The radiograph will show the œsophagus to be dilated above the stenosis ; the walls will appear undulating with regular waves of peristalsis ; and the foreign body, often a pea, will produce a filling defect with a sharp convex margin in the column of barium. Foreign bodies which, by virtue of their

size or sharp projections, become impacted in a normal œsophagus provide little of special interest and, although they are a frequent cause of acute dysphagia, need no further mention.

The accidental drinking of a corrosive substance occurs not uncommonly in this age group and the degree of dysphagia from acute œsophagitis may be very severe. On fluoroscopy the œsophagus appears tightly contracted and the walls are irregular due to ulceration, œdema and spasm. By rest obtained with a temporary gastrostomy, and later, with judicious dilatation, these young patients may show a remarkable improvement provided that one avoids forceful measures ; but recovery is rarely complete, even in mild cases of corrosion, for it is usual to find a simple stricture two or three inches above the diaphragm. This is the site at which injury invariably occurs because it is here that fluid, passing rapidly down the œsophagus, is momentarily held up by muscular contraction. The resulting stricture thus develops at a lower level than the congenital stricture—a point which may assist in their differentiation.

Other strictures caused by trauma, the healing of œsophageal ulcers, certain infectious fevers, and diseases such as syphilis and tuberculosis, present no characteristic radiological features and are only mentioned for the sake of completeness. It should be noted, however, that tuberculous ulceration of the upper alimentary tract is not an uncommon cause of dysphagia in the terminal stages of pulmonary tuberculosis, when the clinical picture is usually obvious and the lung involvement is immediately seen on screening.

THE THIRD DECADE

Achalasia.—The commonest cause of dysphagia in the third decade is achalasia, a disease so well known that only a few radiological features will be mentioned. In its earliest stages radiology provides evidence in support of the current theory that achalasia is caused by a neuro-muscular lesion. Firstly, one finds a spasm affecting a segment about one to two centimetres long, at the lower end of the œsophagus. This segment involves the cardia and the cardiac ampulla or that part of the œsophagus lying in and below the diaphragmatic hiatus.

By careful radiology, folds of gastric mucosa can be defined in this segment, and in one case of achalasia Allison [5] was able, with his clip method, to demonstrate that the mucosal junction lay above the constricted portion (Fig. 4).

Secondly, there is a moderate degree of dilatation above the constriction extending up as far as the aortic arch—in other words, in the segment in which plain muscle is found—but above this level, the dilatation is greater (Fig. 5). This is in direct contradiction to the statement that dilatation occurs first at the lower end, which it certainly does in cases of stricture. After months of continuous

distension the lower half enlarges into a uniform sac but the striped muscle segment may still remain a little wider than the lower segment. When this stage is reached the diaphragm, at the extremes of respiratory excursion, is found to effect a marked alteration in the shape of the dilated œsophagus ; an observation which demonstrates the pliability of the walls and assists in the differentiation from a neoplasm.

Thirdly, no normal peristalsis is observed and if primary waves are seen in the upper portion they do not pass along the plain muscle segment in a normal manner ; for, along 'the borders of the lower segment, are seen small wavy contractions as if the circular fibres alone were making an effort to convey the bolus. Thickening of the muscle wall is generally evident in the radiographs.

Although dysphagia and nocturnal regurgitation are the most characteristic symptoms, it is surprising to find how many patients scarcely notice their difficulty in swallowing. Further, if the crico-pharyngeus muscle, acting as an upper sphincter, functions satisfactorily they may be free from distressing regurgitations. Instead, the large

FIG. 1.—Base of tongue (B)—bulging backwards and downwards as it propels the bolus. Epiglottis (E) turned over.

FIG. 2.—Lipiodol filling the œsophageal " cul-de-sac." Note air in stomach and bowel denoting tracheo-œsophageal fistula.

FIG. 3.—Typical congenital stenosis in adolescent. Shortening of lower segment. Gastric mucosa seen passing through the œsophageal hiatus.

FIG. 4.—Early stage of achalasia. Gastric mucosa seen in narrowed segment.

FIG. 5.—Early stage in achalasia. Note the serrated outline due to small, irregular contractions : wide dilatation of upper segment : thickening of the wall.

FIG. 6.—Shadow on right of mediastinum caused by dilated œsophagus. Bi-lateral atelectasis of the lower lobes with bronchiectasis.

œsophagus may cause other complications such as atelectasis of lung with bronchiectasis, affecting particularly the lower lobes ; or pressure on the heart may give rise to cardio-vascular attacks sometimes terminating in sudden death.

It is well to bear in mind that whenever an opacity, usually with a smooth convex border but sometimes nodular, is seen to encroach on the lung fields from the right border of the sternum, a dilated œsophagus should be suspected. Extension to the left in the superior mediastinum is prevented by the descending aorta and the opacity curves outwards over the right hilum. It may project beyond the right border of the heart, and it is not uncommon to find a nodular shadow in the right cardiophrenic angle when the œsophagus is kinked. If a leading question brings an admission of slight dysphagia of long standing, then the diagnosis of achalasia can usually be made with confidence (Fig. 6).

Treatment by octyl nitrite has produced some remarkable results in children. Our experience is at present very limited but the drug has not been effective in all cases, and therefore, the claim that it can be used to differentiate between simple spasm and achalasia appears unfounded. Whatever the form of treatment a word of warning must

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.
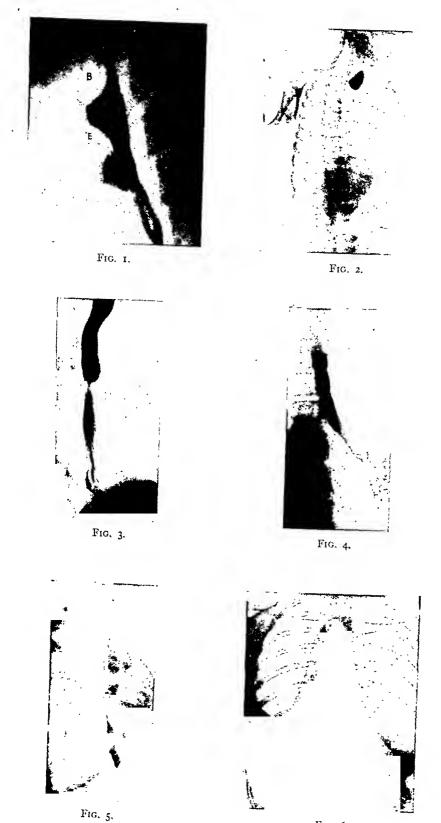
FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG 10.

FIG. 11.

FIG. 12.

be given to those who expect to see a remarkable radiological improvement. The reduction in size of the œsophagus may be quite small and is in no way comparable with the improvement felt by the patient. However, the earlier treatment is begun the greater the improvement because muscle degeneration and fibrosis will not have occurred to any extent.

THE FOURTH AND FIFTH DECADES

Post-cricoid Web.—In this group we find dysphagia occurring in middle-aged women suffering from anæmia of the hypochromic, microcytic type. The signs of the Paterson-Brown Kelly and Plummer-Vinson syndrome, with fissured lips, sore tongue, koilionychia, splenomegaly and achlorhydria may be present and any one of these should forewarn the radiologist to pay special attention to the post-cricoid region.[6, 6a]

It is interesting to recall that Vinson considered the dysphagia to be hysterical; Brown Kelly favoured spasm; while Paterson suggested that a web might exist as well as spasm. On endoscopy

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FIG. 7.—Shelf-like defect in barium column produced by web.

FIG. 8.—Peptic ulcer of œsophagus. Crater seen in narrowed segment with dilated œsophagus above and gastric pouch below. (Semi-erect position.)

FIG. 9.—Irregular contractions of circular fibres producing "functional diverticula."

FIGS. 10 and 11.—Filling defect produced by simple tumour. Note ring shadow: lobulation: smooth external surface.

FIG. 12.—Œsophagus displaced anteriorly by rudimentary left aortic arch.

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the spasm is readily appreciated and those who have seen webs stretching partially across the lumen have drawn attention to the absence of bleeding after their rupture, a feature which may have led to insufficient appreciation of their significance. Careful fluoroscopy may reveal two things—a spasm at the upper end of the œsophagus and a web. The first, a narrowing in the post-cricoid region about one to two centimetres long, is seen in the antero-posterior view. It appears to be caused partly by contraction of the lower fibres of crico-pharyngeus and partly by the terminal bundles of the muscularis propria of the œsophagus.

The second is a small projection from the anterior wall which, as it becomes bigger, juts out into the column of barium like a thin shelf. The webs may be multiple and are commonly situated in the post-cricoid area but may be found at a lower level (Fig. 7).

The formation and structure of a web is debatable because, if it arises from fibrosis it is difficult to explain how it will disappear on iron therapy alone. Degenerative changes in the mucosa occur with iron deficiency and it is possible that, in conjunction with post-cricoid spasm, thin films of desquamating tissue may collect to form a web. The administration of iron, restoring the mucosa to normal, may lead to the relief of spasm and disappearance of the web. One

argument against this explanation is that webs have been found at levels quite remote from the post-cricoid group of muscles.

Sometimes a thicker shelf is seen to project from the posterior wall and this is due to a contraction of the circular fibres of the crico-pharyngeus muscle and is considered to be non-pathological. When, however, the barium is held up by a diaphragm which appears to be a combination of both web and crico-pharyngeus muscle, a more serious view should be taken for it is possible that malignancy may have supervened. This complication is well recognised but one must not forget that the rest of the œsophagus and stomach must be included in the examination, for in one of our cases cancer of the pylorus was found at the same time. It is a wise practice to submit all cases to œsophagoscopy so that not only can malignant disease be excluded but, at the same time, the affected area is dilated giving more rapid relief than is obtained by iron alone.

The Fifth to Seventh Decades

Peptic Ulceration of the Œsophagus and Partial Thoracic Stomach. —Peptic ulceration of the œsophagus, perhaps the most interesting disease in this series, occurs almost equally in men and women, and 70 per cent. of our cases are found in this age group. Except for a large series published by Jackson [7] in 1929, this lesion was a rarity until Briggs, Dick and Hurst [8] described eight cases which they found associated with congenital short œsophagus and partial thoracic stomach. Clerf and Manges [9] were probably the first to record this combination of lesions, but their work has passed unrecognised because the title of their paper made no reference to peptic ulceration.

In five years the Thoracic Surgery Department in Leeds has collected records of fifty cases (including œsophagitis) a figure which becomes of great significance when, as Allison [10] has pointed out, during the same period only fifty cases of carcinoma of the lower end of the œsophagus were found. These figures show that the disease is not uncommon although the incidence may vary in different parts of the country. Its recognition finally depends on œsophagoscopy but one can make a reasonably accurate diagnosis on a careful history and radiological examination.

In our cases the outstanding feature has been dysphagia. The patient, probably a well-nourished individual of the hypersthenic build, will complain that food seems to stick behind the xiphisternum causing pain which may be relieved by eructation or even vomiting. The pain comes on suddenly and often follows the taking of hot, spicy, hard or bulky food. It may become so severe that fluids cannot be swallowed without discomfort. The degree of obstruction varies and may at times, be complete.

Another pain is felt in the epigastrium sometimes striking through to between the shoulders, and this may come on half to one hour after

food. It is aggravated by bending forwards or lying on the right side at night. This pain may be severe, or no worse than heartburn. Many cases give a history of previous gastric ulcer, duodenal ulcer or cholecystitis, and the symptomatology may be confused with the co-existence of these diseases. Hæmatemesis can occur and may be severe.

On examination, the well-nourished appearance, in contrast to the patient with cancer, is most striking. The radiological diagnosis is based on finding certain changes at the lower end of the œsophagus and a gastric pouch above the diaphragm. Briefly, these changes include a stricture from one to six centimetres long, found usually midway between the diaphragm and the bifurcation of the trachea. Above, the œsophagus is a little dilated and tapers fairly abruptly into the stricture. The mucosa shows irregularity due to œsophagitis, or even leucoplakia, and an ulcer niche may project from the stricture. Immediately below the stenosis the lumen expands, and a wide pouch, lined by gastric mucosa, can be demonstrated if a sufficient quantity of barium passes through to fill this pouch in the supine position (Fig. 8).

If it is possible to carry out a test meal investigation, hyperacidity will be found in the majority of cases (Dick and Hurst [11]).

On œsophagoscopy two types of ulceration may be found after dilating the stenosis. One is a deep, circumscribed ulcer with a crater which shows on the radiograph; the other is an extensive superficial ulceration with a firm lower margin within one centimetre of the cardia, and an irregular upper margin with red areas of granulation tissue interspersed with thin white processes of epithelium; areas of more chronic ulceration are mingled with areas of healing. The final diagnosis must rest on œsophagoscopy and biopsy.

Ætiologically the disease is of great interest for it embodies physiological and anatomical problems as well as the general theories of peptic ulceration. Reviewing the pathogenesis we find that there is some structural abnormality which allows free regurgitation of acid gastric juice and pepsin into the œsophagus. There seems, in addition, to be a constitutional liability to hyperchlorhydria and perhaps an ulcer diathesis. It is well recognised that the constant bathing of the duodenum or jejunum with free hydrochloric acid and pepsin will lead to ulceration and the same process occurs in the œsophagus. Islets of heterotopic gastric mucosa, commonly found in the post-cricoid area or just above the cardia, are considered to be of ætiological importance. Dick and Hurst suggested that in cases of peptic ulceration without a hiatus hernia, free acid, secreted by these islets, might collect above the cardia in sufficient quantity to cause ulceration; but it seems only reasonable to suppose that any acid arising from such a small source would be quickly neutralised by saliva. In all our cases a hiatus hernia was present, a point of interest when Jackson reported that in none of his eighty-eight cases, of which only twenty-one

had active ulcers, was there any abnormality of the cardia. Oral and dental sepsis may be contributory factors, but their importance has been exaggerated and it is possible that poor mastication and ill-fitting dentures may exert a more harmful influence. There is no doubt that the most important factor is the structural abnormality which allows free regurgitation into the œsophagus. Hurst and his colleagues stated that the short œsophagus and partial thoracic stomach were congenital defects which led to regurgitation of gastric contents, because the cardiac sphincter—a structure which exists physiologically if not anatomically—lies above the diaphragm and has no longer the support of the diaphragmatic pinchcock. Further, its position at the apex of the fundus nullifies any valve-like action which might exist by virtue of the oblique insertion into the lesser curvature of the stomach. In consequence, any increase in pressure in the upper abdomen, brought about by stooping or lying down, easily overcomes the cardiac sphincter and gastric juice regurgitates into the œsophagus.

Allison *et al.*[5] considered that in the majority of their cases the œsophageal shortening was acquired, a view supported by Harrington[18] who contends that congenital short œsophagus is a rare condition while hiatus hernia, in elderly people, is relatively common. It is important to recall that the exact location of the cardia is by no means settled. Since the work of Arnold[12] in 1835 many opinions have been expressed as to whether there are two pouches at the lower end of the œsophagus—the ampulla phrenica and the ampulla cardiaca— and, if so, which represents the fore-stomach of some herbivorous animals. Exact interpretation of the radiological evidence is not yet forthcoming, but we believe that the junction of the mucosa, although irregular, takes place at a higher level than is generally appreciated and that the infra-diaphragmatic portion of the œsophagus appears, by its behaviour, to be allied more closely to the stomach than to the rest of the œsophagus. If these suppositions are correct the cardia will be situated at or near to the diaphragm.

It is logical to assume that considerable laxity of structures at the diaphragmatic hiatus must be present to facilitate respiratory movement and distension of the œsophagus. Findlay and Brown Kelly[13] in 1931 described a hernia of the cardia through the diaphragmatic hiatus as a normal physiological process in children. This wide range of movement is not observed so readily in the young adult but, as old age approaches, particularly in the hypersthenic type, intra-abdominal pressure increases with adiposity, muscle tone at the diaphragm is lowered and on lying down the cardiac ampulla herniates through the hiatus. This is the pulsion type of hernia, known also as hiatal insufficiency. The stage has now been reached when the structural changes allow free regurgitation, and if inflammation with peptic ulceration in the lower œsophagus follows, then local spasm occurs which affects both the circular and the longitudinal muscle fibres. The segment thus becomes narrowed and shortened and the

plentiful elastic tissue will tend to maintain the deformity. Unless resolution occurs rapidly the resulting fibrosis will ensure that the changes are permanent, making the gastric hernia irreducible and radiologically indistinguishable from a congenital shortening.

We have observed a series of such changes in an infant which gives considerable support to our hypothesis relating to the adult.

In the early stages of this condition the medical treatment is aimed at resting the œsophagus and preventing regurgitation. The patient should sit up as much as possible and sleep with the head of the bed elevated by blocks. The diet and medicines should be similar to those given in the treatment of gastric or duodenal ulceration, except that the meals must be infrequent rather than small and frequent. Only fluids are advised at first and care should be taken to avoid extremes of heat and cold. Dick and Hurst recommend atropine and olive oil before the meal, and a good drink of water after the meal to clear away food débris. Alkalies are given at regular intervals and the sucking of bismuth lozenges is advised.

If the dysphagia is marked careful dilatation under direct vision will give immediate benefit, but recurrence must be expected unless the inflammatory condition improves. If the case proves intractible a jejunostomy or gastrostomy and, ultimately, excision of the affected area will have to be considered.

THE SIXTH DECADE

Pharyngeal Diverticulum.—It is generally in a man over sixty that we find a pharyngeal diverticulum, an abnormality readily and prettily diagnosed by radiology but rarely recognised clinically. A possible reason for this may be that the patients do not express themselves clearly as to how and where their dysphagia affects them. In the early stages it seems that the crico-pharyngeus muscle fails to relax properly during swallowing and this causes a feeling of obstruction in the lower part of the neck. At this stage, the pouch, developing through a weak spot in the posterior pharyngeal wall, is so small that there is neither retention nor regurgitation of food. The radiological appearances, however, are quite distinct and a small diverticulum in which barium will lodge for a short time, is found lying between two muscle bundles—the oblique and circular fibres of crico-pharyngeus. The diverticulum grows but for some time it can be emptied by vigorous deglutitionary efforts. Eventually it gets so big and the channel into the œsophagus becomes so distorted that it is only with difficulty that food can be swallowed. Fluid and food remain in the pouch causing discomfort and salivation until the patient obtains relief by forcing the contents back into the mouth. So, in the late stages, the patients complain mostly of the exhaustive efforts at swallowing which are required to get food down, and that fluids may cause more trouble than solids. They are compelled to regurgitate their food and when

it returns they may recognise undigested remnants of a meal taken, perhaps, some days previously.

The neck may look full but one does not often get a history of a swelling following meals. A large pouch always contains food and fluid, and can be recognised immediately by the fluid level lying just anterior to the sixth or seventh cervical vertebræ. Surgical treatment of these cases by one-stage operation is eminently satisfactory, but they should be carefully watched, and any tendency to recurrence may be avoided by dilatation of the crico-pharyngeal region through the œsophagoscope.

Traction—Pulsion-Traction Diverticula.—The ordinary small traction or pulsion-traction diverticula do not give rise to symptoms, and in none of three cases of large congenital diverticula in the lower half of the œsophagus was there any complaint of dysphagia.

Tertiary Contractions with Functional Diverticula.—An unusual condition, recently described by Templeton [14] as " tertiary contractions of the œsophagus with functional diverticula," may cause difficulty in swallowing. This interesting lesion affects elderly men and is recognised by abnormal contractions of the circular muscle of the lower half of the œsophagus set up by swallowing.

One patient, a man of 66, complained that he was unable to swallow either solids of fluids. He said the dysphagia was of sudden onset and he felt an obstruction behind the manubrium sterni. The condition remained for three days when it suddenly disappeared after taking a drink of water. He had suffered a similar attack eleven months previously. When examined with barium emulsion the upper segment of the œsophagus appeared normal, but, as the barium filled the middle and lower segments, it appeared twisted into knots. The term corkscrew œsophagus has been applied to it in several countries and this will, without doubt, gain acceptance here. There was very little muscular activity but the spasms made the loculations stand out like diverticula (Fig. 9). In this case, which has been examined on several occasions over a period of almost a year, the deformities have remained constant, but true diverticula may eventually form. On endoscopy, Allison found the mucous membrane thrown into loose folds, but no other abnormality.

In another man very active contraction of the circular muscle segments was observed after each mouthful and these continued until the lumen was almost clear of barium, when the œsophagus resumed a normal appearance.

It is evident that a neuro-muscular disorder is present and one explanation is that contraction occurs in alternate segments of circular muscle so that the intervening portions bulge out like diverticula. Similar changes are said to be found in Parkinson's disease but this has not yet been confirmed. Milder cases causing no dysphagia are found and these resemble the irregular contractions described in achalasia.

Vallecular Dysphagia.—The term vallecular dysphagia [15] was used to describe cases in which no abnormality could be found other than a delay in emptying the valleculæ. Barium often lodges for quite an appreciable time in the valleculæ and it is difficult to determine when such a condition becomes pathological.

Welin [16] recorded five cases of dysphagia, accompanied by a feeling of a foreign body in the throat, in which the only abnormal finding was the slow, jerky return of the epiglottis to the erect position after swallowing. I have observed two similar cases, but again, there is considerable variation in the normal subject, and it is difficult to assess the significance of such an observation. A study of this region,[17] however, provides us with ample evidence that the physiologists' conception of the epiglottis turning over to protect the laryngeal aditus is quite true, and although, very occasionally, one sees the epiglottis remain upright, Barclay's theory cannot be substantiated (Fig. 1).

Benign Tumours.—Benign tumours of the œsophagus are almost too rare to be included in this series, but they present certain characteristic features which, if correctly appreciated, may avoid a disastrous error in diagnosis. Of the tumours described, the leiomyoma and fibroma predominate. They are slow growing, often lobulated and tend to remain submucosal. Clinically they cause dysphagia, substernal pain, often eased by regurgitations and, at times, vomiting. The onset of symptoms is so gradual that some years may elapse before the patient seeks advice, but during this period no significant loss of weight will have been noticed. The principal radiological feature is the finding of a soft-tissue mass, which projects into the lumen of the œsophagus, diverting and sometimes forking the stream of barium. The lobular shape of the tumour, jutting into the lumen, may be evident, but the surfaces appear smooth and the mucosa appears intact. Traces of the normal folds may be seen at the upper and lower margins, spreading out and flattening as they pass over the mass. At the lower margin the folds converge on to a ring shadow which denotes the infolding of the mucosa at the junction of the tumour and the normal wall. The external border of the soft-tissue mass is smooth and merges imperceptibly into the œsophageal walls above and below (Figs. 10 and 11). In one case examined by us, the tumour, arising near the cardia, had caused so much dilatation and kinking that a diagnosis of achalasia was made.

Nervous Lesions.—A group of diseases, such as bulbar paralysis, botulism, diphtheria and myasthenia gravis, may bring about dysphagia by paralysing one or more of the muscles of deglutition or by causing loss of sensation. These cases are rarely seen and examination with barium is not recommended because it only adds to the risk of aspiration pneumonia. It is of interest, however, to record that in the only case of bulbar paralysis examined by us the barium emulsion, despite the complete absence of any swallowing movements, trickled down

the lateral channels into the œsophagus and none entered the larynx.

Extrinsic Pressure from Cardio-Vascular Causes.—Dysphagia due to extrinsic pressure on the œsophagus is so frequently discovered that the possible causes are too numerous to discuss here.   There is, however, one rarity which might be mentioned on account of its embryological interest.   When the aorta develops from the right primitive arch instead of the left, the rudiment of the left arch may project like a diverticulum behind the œsophagus, displacing it forwards (Fig. 12). This may not give rise to any symptoms until, perhaps with senescence, atheromatous changes kink the œsophagus sufficiently to cause dysphagia.

In conclusion, it is worth mentioning how often one sees the œsophagus not only kinked by adhesions to a dense atheromatous aorta, but pounded between it and a big, heaving left ventricle ; that such patients so infrequently complain of dysphagia is a great testimonial to the resilience and versatility of the œsophagus.

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THE EXPERIENCES OF AN OTOLOGIST ON ACTIVE SERVICE *

By J. P. STEWART, M.D., F.R.C.S.E.

I HAVE chosen as the subject for this lecture " The Experiences of an Otologist on Active Service " because those experiences will help to give you an idea of the extent of the ear, nose and throat services that were made available to the Army, and also of the life of an otologist. They were, I suppose, very similar to those of the greater number of otologists.

GENERAL

An otologist in the Army is the official designation for an ear, nose and throat specialist and not, as the name suggests, for purely an ear specialist.

What were the qualities required for such a position ? One had to become adjusted to new surroundings, new ways of living and to a lesser extent, new ways of thinking, therefore it was essential that one should be *adaptable*. Again, a new discipline had entered our lives, which at times, especially to the senior man, was irksome, so a *sense of humour* was also very necessary. *Initiative* too was required.

The equipment for an ear, nose and throat department was generous and well thought out. The sets of instruments at the beginning of the war were, it seemed, on too generous a scale. Later they were much cut down yet always remained sufficient. They were of the finest quality and workmanship, of stainless steel and far above the standard of those used in the Canadian hospitals. Very practical endoscopic sets were held by those hospitals placed in strategic positions and, when possible, were placed in the charge of an experienced endoscopist.

The ear, nose and throat cases were kept together and special wards were made available for them. The number of beds depended on the demand. Generally 50 beds were allocated to a busy clinic, but in the B.L.A. the clinic, of which I was in charge, maintained 100 beds for this speciality. I would point out that a larger number of beds is required in the Army than in civilian hospital practice owing to waiting lists for admission being impracticable because of the mobility of the troops ; whether it is possible for the soldier to be released from his duties ; and also on account of the difficulties of transport and communications. This perhaps applied more to conditions in the field. For these reasons I scrapped any waiting list to which I fell heir, and was able to maintain an efficient service without one.

* A Honyman Gillespie Lecture given in the Royal Infirmary, 14th February 1946.

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The nursing staff of an ear, nose and throat department consisted of two fully trained sisters in charge of the ward, with a number of nursing orderlies, while a senior V.A.D. nurse and stenographer assisted in the out-patient department. The patients were well looked after. Their bed linen was always clean and their food plentiful, of first-class quality, and served hot. I made a point of visiting the ward kitchen when dinners arrived from the central cookhouse so I speak from personal experience, and I may mention that during all my time in the Army I never had one complaint from a patient concerning the quality or quantity of his food.

The type of case encountered depended very largely on geographical position and upon whether or not active hostilities were in progress. In the United Kingdom the work was largely routine and very similar to that carried out in civil hospital practice. In the East one ran across many cases of interest. In Persia I saw two cases of Rhinosporidiosis, several of leprosy, and a number suffering from nerve deafness which occurred as one of the early symptoms in typhus. The actual war casualties were intensely interesting and presented many an anatomical problem.

As regards the incidence of ear, nose and throat cases, I have taken a series of 5676 cases and found that they comprised 2865 (approximately 50 per cent.) diseases of the ear, 1861 (approximately 33 per cent.) diseases of the nose and 950 (approximately 17 per cent.) throat cases. In looking at these figures it will be seen that the ear cases totalled half the whole number of the series and it might be justifiably concluded from this that the examination of the ears on recruitment should have been more carefully done, as a large number were due to chronic suppuration of the middle ear spaces. A proportion of them therefore should have been rejected.

I have divided this lecture somewhat arbitrarily into three phases. The first phase will deal with the period from mobilisation to the fall of France, the second, from that catastrophe to the time of my return from the East, and the third, will recount my experiences in a static military hospital and in the B.L.A. up to the time of demobilisation.

THE FIRST PHASE

On Thursday, 31st August 1939, I had been operating in the country and on my way home, passing through a village, I caught sight of a newspaper poster outside a small shop on which was emblazoned " General Mobilisation." I knew then that my civilian activities would cease and I speculated on how long the war would possibly last, and tried to imagine the changes which were about to occur in my hitherto ordered life. On my return home mobilisation papers were awaiting me and you can imagine the rush of closing down a busy practice, packing up, and journeying to the extreme south of England all in the space of twenty-four hours. On arrival at

my mobilisation centre at Tidworth there was inevitable confusion, in a mess, built to accommodate in peace time some dozen officers at most, where well over a hundred had suddenly arrived. We got sorted out eventually, although it was lucky to have even a stretcher to sleep on! The first few days were extremely trying as it was a matter of killing time, and one could not venture far from the barracks as movement orders were rapidly coming in. The art of killing time is a highly specialised one and difficult to acquire—fortunately I had to do very little of it. At the end of my first week I was asked to take on the duties of otologist at Tidworth Military Hospital until my Unit was ready to go abroad. The work was largely similar to that which I had just left—more or less routine. The physical standard of the troops at the beginning of the war was very high and the work was therefore mainly seasonal. The large number of cases of otitis externa and chronic suppuration of the middle ear, which were to loom so largely in the succeeding years, were as yet few. A certain number of retired officers now re-employed had to be weeded out. One particular case comes to mind. This was a rather elderly-looking man, an R.T.O. who was sent to me rather urgently on account of hardness of hearing. Apparently he was experiencing some difficulty on the telephone. He had been ordered by telephone, to send a train to some place in the West of England and just failed to pick up the location. In his anxiety to conceal his deafness he guessed it to be Southampton—a common destination in these early days—a rather unfortunate guess, and I'm afraid that was the end of his career in transportation.

The afternoons were devoted to general training—route marches, gas-mask drill, lectures, etc., and in fact, most things that are calculated to turn a doctor into a soldier. This was where a sense of humour was needed. Still, morale was high and we were only awaiting the day to go abroad.

We landed at Cherbourg about the middle of January 1940 and proceeded to Rouen to open a hospital there. We were a 1200-bedded hospital and rather unfortunately the medical and the surgical sides were accommodated in two different places some little distance apart. The surgical component and the administrative side stayed together and this part of the hospital was sited in an old chateau standing in extensive grounds. Most of the wards were under canvas and my own department was housed in a marquee adjoining that of the eye department with a central separate portion used as a common waiting-room for the two departments. It is extraordinary how one can improvise. I soon had a spacious and lavishly fitted up examination room—my dark room for transillumination was made of packing cases with a large black curtain over its entrance, and served most efficiently. Cases soon arrived and we became very busy mostly with routine work, as active fighting had not yet broken out. There were two operating theatres housed in the chateau. One of them

was set up in the large kitchen of this building. The massive range was boarded up in such a way that its top provided an ideal instrument table. The floor was already tiled, and when the Royal Engineers had fitted it out with modern electric lighting (some parts had even concealed lighting), put in washhand basins and painted it in a restful green shade, we all thought it could hold its own with any theatre in a peacetime hospital. An adjoining smaller kitchen served as an anaesthetic room. I was privileged to perform the first operation in the hospital—a radical mastoid in a case of an acute exacerbation of a chronic suppuration of the middle ear.

Soon after this, the storm burst and, alas for our high hopes, this fine hospital which we had all worked so hard to establish, from then on functioned as an advanced dressing station. We received casualties from the Somme, many from the gallant 51st Division. Ear, nose and throat work ceased, of course, and I worked as a general surgeon in charge of one of the surgical teams. I must admit I felt somewhat nervous as to what cases were coming my way, and it was with considerable trepidation that I tackled a case of complete rupture of the transverse colon due to blast injury. However, I had as my assistant the pathologist, a breezy Irishman who always complained that my incisions were too small and urged that at least a modified symphysis menti to symphysis pubis incision would give better access ! The serious cases were retained for twenty-four hours while the less serious ones were only kept until the next ambulance convoy left— a matter of a few hours at most. Blood for transfusion was mostly obtained from the personnel of our unit as very little reached us from the blood bank. This I considered a very bad practice as all these men were working extremely hard, and it was only a matter of time before the unit was bled white. I also thought then that blood transfusions were given too readily.

I shall never forget the sight that met my eyes one early morning when, after a rather exhausting night of operating, I threw open the theatre window to inhale the lovely morning air and gazed out on spacious lawns covered with beds occupied by casualties—so many were coming to us that we had no room for them under cover. One afternoon shortly after this the Area Commandant looked in at the hospital to inform us that he was moving his Headquarters rather hurriedly and advised us to evacuate all our patients without delay and close our hospital, as the Boche were in the immediate vicinity. Fortunately we had anticipated this move and had kept our bed-patients down to a bare minimum so that we were able to evacuate all our remaining cases with the exception of a very few who were too ill to move. When this had been accomplished we ourselves got under way and after a somewhat exciting trip to the south-west coast of France we embarked at St Nazaire on 17th June and reached Falmouth shortly after.

The Second Phase

After our arrival in the United Kingdom from France, things were rather disorganised from the hospital point of view. Many hospitals from the B.E.F. had arrived back without equipment, and a breathing space was required in which to re-equip and generally sort out the tangle. Some of these hospitals were called upon to send out officers on temporary duties. This was rather welcomed, and in due course my turn came and I was posted as a Regimental Medical Officer to an A.A. Training Regiment. I stayed there for two months and a very happy and instructive time I spent with them. I was of course especially interested in the ear, nose and throat cases of which there was quite a number. I was able when necessary to carry out surgical treatment at the local E.M.S. hospital through the courtesy of Mr R. L. Stewart who was surgeon-in-chief. In my spare time I did a number of civilian ear, nose and throat cases at the Dunfermline and West Fife Hospital. After this bus-man's holiday I was instructed to join a general hospital in the North-West of England as otologist. The buildings occupied by this hospital had been used as a training college for female teachers. They made an ideal hospital with the large class-rooms converted into well-ventilated wards. The hospital was a busy one and situated at a key point. When I took over, the ear, nose and throat department had not been functioning very long and became steadily busier as time went on. In the space of seventeen months I saw 2729 new cases and performed 667 operations. Hospitals were constantly forming in our buildings and I had the good fortune to have with me for a time two ear, nose and throat colleagues, R. R. Simpson of Hull Royal Infirmary and W. Daggett of King's College Hospital with whom an interchange of views and ideas on cases was most profitable. The hospital was a progressive one and joint clinical meetings with the local civil practitioners were held at regular intervals. Our services were called upon to see and operate on patients in the local civil hospital. The air blitz was then at its height and we relieved the visiting specialists to enable them to devote their full energies to their own hospitals in Liverpool which was at that time taking severe punishment. I devoted a certain amount of time to research and published, in association with the bacteriologist, Austin Nimmo Smith, a paper on observations and treatment of Vincent's Infection of the Tonsils. I also investigated from every angle a series of 100 cases of otitis externa—a condition which was becoming increasingly common.

In May 1942 our orders arrived to proceed to the East. The hospital continued to function until a week or two before embarkation. The voyage to Suez via Capetown occupied the best part of two months and I should like to mention that the kindness we received from the people of Capetown was almost unbelievable. During the journey we kept fit with physical training and deck games. Lectures

by the specialists were given each day to the hospital staff while the other ranks also received regular talks of instruction. To illustrate the varied life of an otologist—I was appointed Medical Officer to a series of boxing contests held on the troopship. I had a very fine seat at the ringside, at times unpleasantly near to the boxers, and attended to the injured and the knock-outs. On arrival in Egypt we went to Quassasin on the banks of Sweet-water Canal—I have often wondered why it was called Sweet-water Canal as the natives performed every conceivable office of nature into it. The hospital was held in reserve, and after the El Alamein show we received orders for Persia, as the German drive through the Caucasus was threatening that country. But for the epic defence of Stalingrad, war must inevitably have overtaken that land. We embarked again at Suez and disembarked at Basra, spending some little time in camp on the desert about fifteen miles from that port. I was fortunate in missing most of this trying, scorching time of waiting because I was posted for temporary work in a combined general hospital (partly made up of I.M.S. and partly R.A.M.C.) at Ahwaz, a small oil and garrison Persian town situated at the base of the foothills at some distance from the coast, with a day temperature of 130° F. I was then sent as Senior Medical Officer in charge of a large party of Polish civilian refugees, in transit from Russia to Mombassa, during their sea voyage to India. Again one had to be adaptable as my services were sought for cases as widely diverse as trachoma (of which there were many) and those of obstetrics. I left the refugees at Karachi and while awaiting a passage back to Iraq, was attached to the British General Hospital at Karachi where I did some general surgery for a week or two.

I arrived back in Basra in time to join my hospital which was just about to proceed to Teheran. After a journey by road through mountain passes terrifying in their grandeur, we reached Teheran and took over a partially finished hospital which was being built by the Germans for the Persian Government. It was an extremely modern building embodying all the latest improvements in hospital planning, and was capable of accommodating 600 beds along with the administrative offices and Sisters' Home. The male permanent staff were under canvas, and as Teheran is 4000 feet up, living conditions in a rather severe winter were not comfortable and heating was very inadequate. There was a block in the hospital building which contained six operating theatres of the latest design. I was allotted one of those for my special work. Immediately adjoining it was the ear, nose and throat ward of some 40 beds and my out-patient department. It made an ideal ear, nose and throat unit. Additional beds for my patients were located in the spacious hospital compound where another 400 beds were housed under canvas. Some hundreds of yards away was a Convalescent Camp, so that it was easy for patients discharged there to attend my department for continuation of treatment. During my stay in Teheran I saw 967 new cases,

performed 220 operations, and carried out an investigation on the operative treatment of acute tonsillitis on a series of 50 cases.   These patients at the time of operation were only just recovering from an acute attack of tonsillitis and were unfit for discharge from hospital. The time taken for the patient to recover from his operation was almost the same, in some cases shorter, as if he had been treated along conservative lines.   In addition to duties in my own hospital I attended and operated on ear, nose and throat cases in a Combined General Hospital wholly under canvas, and in an Indian General Hospital accommodated in part of the Skoda small arms factory and utilised almost wholly for Polish civilian refugees.   During the typhus epidemic which raged in Teheran in the late spring of 1943 the Combined General Hospital, there was loaned temporarily to the Persian Government for the reception and nursing of the civilian typhus cases. I examined quite a number of those typhus cases who had also urgent ear, nose and throat complications.   I was able to make a tour of the Teheran civil hospitals and was much impressed by their buildings and equipment, again of course of German origin.   I was *not* impressed, however, by the staffs of those hospitals even though some had been trained in hospitals on the continent.   Their standard of work was low and rather crude.   I happened into one ward where a poor patient had been having an amœbic abscess of his liver evacuated.   A crowd of white-coated medicos surrounded the bed of the unwilling and struggling patient and some of them were even standing on the patient's bed, whether to keep him from hitting the ceiling or to obtain a good vantage point, I know not.   I saw many cases of very advanced untreated malignant disease which had only just been admitted to hospital for treatment.   Tertiary syphilitic cases with magnificent gummatous lesions were also multitudinous.   At one teaching hospital at which our procession of cars drew up, I saw a young lad of some 16 years (a bundle of rags and covered with flies) lying under a bush. He had barely enough strength to occasionally raise his arms to brush the flies off his face.   After our tour of the hospital I noticed two hospital orderlies carry this poor wretch off to some outhouse, or more likely to some spot just out of our sight.   An Armenian doctor who acted as our guide told me that this lad had been lying there for the last two days and it was only because Europeans were visiting the hospital that they had removed him as they thought we might get a wrong impression.   Otherwise he would have been left to die where he was !

I did, however, come across Max Mayer of international reputation, formerly professor of ear, nose and throat at Würtemburg, later at Istanbul, now professor of that speciality at Teheran University.   He received me very cordially and I spent a most interesting time with him going over his microscopical slides of many rare and unique specimens.   I also had the opportunity of visiting the Faculty of Medicine at Teheran University—again a glorious modern . edifice

with *de luxe* lecture theatres and laboratories.   Apart from the morbid anatomy and bacteriological sections, which appeared to be turning out good work, I was not impressed by the knowledge of the systematic teaching staff.   To be fair, however, we must not forget that this is a country only just emerging from mediæval times and not therefore to be judged too harshly.

With the turn of the tide of war Paiforce was radically reduced, and as our hospital was no longer required, we retraced our steps to Egypt.   This time we went overland through Iraq, Transjordan and Palestine to fetch up at a Transit Camp at Ikingi, just outside Alexandria.   Shortly after, we embarked from that port and made the journey home through the Mediterranean thus completing the round trip.

The Third Phase

After one or two temporary ear, nose and throat jobs, including one at the Isle of Man where some strenuous work was accomplished in dealing with an accumulation of service and internee cases, I was posted to the Cambridge Military Hospital at Aldershot—a hospital with high traditions.   At that time it was the most outstanding of the permanent Royal Army Medical Corps hospital establishments and was run very much on the lines of the Edinburgh Royal Infirmary. We were given a free hand to get on with our work and had every assistance from our Commanding Officer.   The hospital was fortunate in having a particularly able staff and the output of work was of a high standard.   In addition to my duties I was responsible, as I had been in all my hospitals, for the teaching of a trainee otologist and this task was made easier by having to deal with keen and willing pupils.   The time I spent in Aldershot was during the months prior to D-day when there was a large concentration of troops in the immediate neighbourhood and I was kept extremely busy not only with the ordinary routine work but also in weeding out ear, nose and throat cases unsuited for the campaign which was imminent.   It was in this hospital that I was first able to utilise Penicillin in the treatment of patients and I got a thorough knowledge of its uses and limitations from the very excellent advisory bacteriological unit which maintained this service.   The following figures will give some idea of the scope of my work there during eight months—3138 cases were seen for the first time with 2912 re-attendances and 386 patients were operated upon.

I was beginning to grow very weary of home service and much to my delight orders came through in November to join the B.L.A. I journeyed to Ostend in the company of about fifty other specialists —surely one of the largest drafts of specialists.   On arrival at Ostend we took our place in the long column of troops that marched through the town en route for the transit camp.   I regret to say that this body of learned men presented a very sorry sight in an otherwise ordered procession.   As we swung through the streets lined by the inhabitants,

the famous remark of the Duke of Wellington, as he surveyed some freshly arrived reinforcements, came to mind—" I don't know what effect these troops may have on the enemy but by God they terrify me."

I was posted to a general hospital at Duffel midway between Antwerp and Brussels and took charge of the ear, nose and throat department there. The port of Antwerp was just opening up and was being subjected to a heavy bombardment with V1 and V2 projectiles so that in addition to ordinary ear, nose and throat cases we received many with wounds in this special region. Patients also came from Walcheren Island. We had, in charge of our medical division, that most untiring and enthusiastic teacher, Melville Arnott, who rapidly organised a very comprehensive post-graduate programme. Such was the reputation of our hospital that it soon became known as Duffel University. Early in February 1945 I was appointed Adviser in Oto-Rhino-Laryngology to the B.L.A. and left Duffel for Brussels where Medical Headquarters were established. My duties now were partly clinical and partly administrative. I was attached to a large general hospital where, along with a graded otologist, I was responsible for a large ear, nose and throat department with 100 beds. This hospital was located on a key point on the lines of communication and as large numbers of casualties from the front first staged here, one had the opportunity of attending to many fresh cases of wounds of the ear, nose and throat. Difficult cases also were referred to me for a second opinion in my capacity as Adviser, and of course there were the ordinary routine cases. We were the only ear, nose and throat unit in a group of four general hospitals so cases were numerous. Penicillin was in generous supply and great experience was gained in its use. In three months 1340 new cases were examined and 173 operations performed. In order to cope with large operation lists we utilised two tables in the theatre which worked very well. All the instruments stood on a central table from which the operator selected those he required. This was very convenient and saved much time and labour. My administrative duties were to advise on all matters pertaining to ear, nose and throat dispositions. I had to tour round the various hospitals and ear, nose and throat clinics to ascertain that their particular service was running smoothly and that provision was made for adequate treatment of ear, nose and throat cases occurring in the troops in the B.L.A. Nine otologists functioned in the British general hospitals, with some further seven otologists in the Canadian general hospitals. Excellent relations and helpful co-operation were maintained between the British and Canadian units. The American hospitals were also very helpful in dealing with emergencies which occurred among the comparatively small number of British troops remaining in their zone. Each otologist worked on an area basis and was responsible for a group of hospitals. These otologists were young, and keen men who made an excellent team and kept up a high standard of work in our speciality.

Shortly before demobilisation I made a tour of the general hospitals then being established in Germany. The set-up and distribution of the ear, nose and throat clinics was good and the men of the B.A.O.R. should be well looked after. I was amazed at the havoc I saw in Hamburg and Bremen, while the remains of Wesel on the Rhine had to be seen to be believed. One could not but feel some satisfaction, looking back through the years to our hasty and ignominious departure from France in 1940.

One evening, a week or two after my visit to Germany, as I was driving down to Ostend with my demobilisation papers in my pocket, I passed by several roadside cemeteries in the making with hosts of white crosses in orderly rows already there. The rather excited feeling of the prospect of an early return to civil life suddenly departed and a sadness took its place. We were leaving behind comrades for whom there was no return.

CONCLUSIONS

To conclude, the standard of ear, nose and throat work in the Army during the late war, in my opinion, was high. In the B.E.F. the otologists were men of established reputation and position on the staff of our leading hospitals, and who, prior to the war, were already on the Reserve of officers. Throughout the years of war it was inevitable that this strong concentration should be watered down by the incorporation of younger men of less experience, but these were diligent and rapidly gained experience and justified the confidence placed in them.

From my own point of view, far from having spent six years of wasted endeavour, I was enriched by all my varied experiences and opportunities. I emerged from it having accumulated a wealth of knowledge of my own speciality and with a new and broader conception of life.

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MENINGOCÒCCÆMIA

PART I. THREE CASES AND A HISTORICAL REVIEW

By W. R. LOGAN, M.D., F.R.C.P.E., D.P.H.

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THE term meningococcæmia is a convenient one to describe those cases of meningococcus infection in which there is typically a more or less intermittent bacteræmia with arthralgias and polymorph skin lesions. It may occur without meningitis, preceding meningitis, or following the subsidence of meningitis. Synonyms for the condition are " chronic or subacute meningococcal septicæmia or bacteræmia," the " pseudo-malarial meningococcæmia " of some of the French writers, and the " lenta-form of meningococcal septicæmia " of some of the German writers. The term septicæmia is not a good one for this condition, in which invasion of the blood stream is usually periodic and of brief duration. The word chronic is also not quite accurate, though convenient, as there is actually a succession of acute exacerbations or relapses.

The acute or fulminating variety of meningococcal septicæmia with adrenal hæmorrhage, which is included in the " Waterhouse-Friderichsen syndrome " (1911 and 1918), a term doing little justice to earlier workers, such as Graham-Little (1901) and Andrewes (1906), is an entirely different condition, and the word meningococcæmia as used here refers purely to the intermittent and long-enduring variety.

HISTORICAL

Cases of chronic meningococcal septicæmia or bacteræmia have been recognised for over forty years. The first was described by Salomon (1902), and it was a classical case which can be taken as typical of the condition. The patient was a woman of thirty-two who was admitted to the Frankfurt Hospital on 3rd August 1901 with a history of having been taken ill on 30th July with pains and swellings in the joints. On the following day she had shivering, fever, and an eruption chiefly on the hands and feet. On admission she was found to have spots varying from 50 pfennig size to the size of a mark, slightly raised above the surface, paling on pressure ; others had a red centre. The spleen was palpable. She developed labial herpes. Two blood cultures were positive for meningococci. Salomon said that the appearance of many of the spots recalled a septic exanthem with its capillary emboli. The eruption was pleomorphic and later was sometimes like a syphilitic roseola, and still later like a typhoid roseola ; other lesions were like bug bites. The temperature was intermittent of the quotidian type. The skin lesions came out in crops. Meningitis developed about 20th to 27th September, that is

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after about two months of illness. The patient recovered. This patient had thus the syndrome recognised later to be typical of this condition: the intermittent temperature, arthralgias, and multiform skin eruption including papules, coming out in crops with the pyrexial periods.

Martini and Rohde (1905) described a case in a sailor at Wilhelmshaven, but meningitis developed in four days, so that this case was atypical. A case briefly described by Follet and Sacquépée (1906) showed intermittent pyrexia for some weeks following cerebrospinal meningitis. Liebermeister (1908) published a typical case which, like Salomon's, was fully observed and described. There were five positive blood cultures and no meningitis. The illness lasted about four months, with recovery.

The first American case was that of Bovaird (1909), a girl of fifteen years, who developed irido-cyclitis and recovered, but with loss of sight of the right eye. There was slight or doubtful meningitis.

Netter (1909) had a case of meningococcal bacteræmia without meningitis in a child of six, sister of a case of cerebrospinal meningitis. This was not a typical case of chronic meningococcæmia, but rather one of infection aborted by serum. It was, however, the starting point of interest among the Paris physicians, led by Netter, in meningococcæmia. A series of cases was published before and during the 1914-1918 war in the *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, beginning with two fully described cases published by Monziols and Loiseleur (1910), another by Loiseleur and Monziols (1910), and one by Chevrel and Bourdinière (1910). These and further papers by other observers were read before the Paris Society and published in its Bulletins along with the discussions which took place, in which Netter usually took a leading part. It was unfortunate that these French papers were nearly all published in the Bulletins as it is obvious from the later German papers that observers in that country had not had access to them, while many workers in this country also had evidently not read them. Some of the French papers also which appeared at the end of that war were published as M.D. theses of the Universities of Paris and Lyons, and these also were difficult to obtain. This seems to be the explanation of the curious fact that this condition, such a source of interest and discussion in medical circles in France, and particularly in Paris and Lyons, twenty-five to thirty-five years ago, was very largely overlooked in the rest of the world till comparatively recent times. It is true that towards the end of the 1914-1918 war a few lectures and papers were published in the French supplement of the *Lancet*, and Netter republished one of his French papers in the *British Journal of Children's Diseases* in 1918. It is quite certain that unrecognised cases must have occurred in Britain and America during the epidemics of that war. Some of the numerous cases diagnosed as myalgia, and rheumatism must almost certainly, in the light of our present

knowledge, have been meningococcal infection. In the inter-war period with its diminution in meningococcal epidemics, cases of meningococcæmia naturally became more rare.

The first case observed in the Far East was reported by Sakai (1913) from Tokio. In Germany, Bittorf (1915) published four atypical cases in which there was a septicæmia of only a few days before the onset of meningitis, and a typical case in 1916. Svestka (1915) published a Polish case, and Bray (1915) the second American case six years after the first. The first British case was described by Elliott (1916). The patient, a soldier, was admitted to the Glasgow Fever Hospital, Ruchill, with a provisional diagnosis of typhus. His skin lesions were of an unusually hæmorrhagic type, and Elliott was struck with the resemblance between them and those seen in fulminating cerebrospinal meningitis. Lumbar puncture fluid was normal. The man recovered after six weeks' illness. The second British case was published by Marshall Findlay (1919). He was a sailor who developed parotitis and pericarditis, as well as arthritis ; there was no meningitis. . He died on the twenty-seventh day. Two blood cultures had been negative, but the meningococcus was obtained post-mortem from the pericardium. The first cases published in Italy were those of Dal Canton (1916), and Morpurgo and Ferrio (1917).

The condition was beginning to be recognised in Britain and America, and Herrick (1919) described briefly four cases occurring in the course of the meningitis epidemic at Camp Jackson, and Rolleston (1919) in his often quoted Lumleian lectures analysed the different varieties of meningococcic septicæmia and some of the published cases.

In America, Morgan (1921) wrote a review of the condition covering most of the earlier papers, and Dock (1924) analysed 68 reported cases without, however, giving a bibliography. Gulland and the writer (1925) published the third British case, in which there were no skin lesions or joint pains. Interest in the condition was revived in Germany by Friedemann and Deicher's (1926) paper, and Kennedy (1926) described four British army cases, including one of two years and four months almost continuous illness. Another British case was that of Gardiner (1928) in which there was irido-choroiditis as well as suppurating joints, and two others were published by Stote (1929). The French workers had been publishing cases from time to time usually to call attention to some new form of treatment. In 1930 Lundholm and Ströman (1929-1930) published the first Scandinavian case. Stevenson (1931) reported another British case with endocarditis, which was noteworthy for its very careful and detailed post-mortem examination. Three others were described by Stewart-Wallace (1936). Among the American papers published during this period, the most important was that of Appelbaum (1937) containing a full description of 15 cases all observed by himself.

In the following year Lambie (1938) published the first Australian case. In the same year, in America, Carbonell and Campbell (1938) published 2 cases, and analysed 30 cases occurring in the American literature, with special relation to the occurrence of endocarditis. Heinle (1939) described 5 American cases in detail.

With the outbreak of war, and occurrence of epidemics of meningitis, cases became much more frequent and the various series reported by Stott and Copeman (1940), Dickson, McKinnon, Magner and McGillivray (1941), Copeman (1942), and Daniels, Solomon and Jaquette (1943) may be mentioned. Moss (1940) reported two more Australian cases, and Javett and Sachs (1942) one from South Africa. Campbell (1943) published 3 fresh cases and reviewed 85 cases occurring chiefly in the American literature.

References to other papers will be found in the bibliography. To these may be added 3 new cases which have been investigated by the author :—

CASE 1.—M. C., aged 17, laundryworker, was admitted to the late Dr J. D. Comrie's ward in the Royal Infirmary on 5th June 1931. Sixteen days previously she had begun to feel increasing stiffness in the back of the legs ; then they became painful. The wrists next became stiff and painful and she was unable to work. She went to bed because her legs were sore even when she was sitting. Treatment by salicylates did not produce improvement. She was otherwise well save for loss of appetite ; there was no sore throat, headache or malaise, she did not feel hot, and had no shivering or sweating.

On admission her temperature was 101° ; there was no swelling of the joints, but there was pain on movement of the legs, and of the right wrist and shoulder. She was provisionally diagnosed as subacute rheumatism and treated with salicylates and atoquinol without effect. There was irregularly intermittent pyrexia, of for the most part rather low grade, the intervals between elevations varying from one to five days. This pyrexia continued till 14th August, after which there was no further rise. There were higher peaks on 20th and 22nd July when the temperature reached 103°, the first with headache and a slight rigor. Between 4th and 11th August there were five rises to about 102°. Shivering was as a rule not marked, and there was not much sweating.

Skin lesions were observed on three occasions : on admission there were several purplish discolourations varying in size from a threepenny bit to a shilling on the extensor surfaces of both legs ; these faded in a few days. On 30th June a small red subcutaneous nodule appeared over the left elbow. On 5th August during the phase of greater pyrexia an erythematous rash appeared on hands, forearms and legs ; there was no pyrexia on the day that it first appeared.

All through the illness the patient continued to have pain in the joints, at first in the right arm and wrist, and right knee and hip, later chiefly in knees and ankles. There were effusions, not very marked, first in the right knee joint and later in both knees and both ankle joints. These effusions persisted to a certain extent right up to 29th September when she was sent to the Convalescent House, and she still had occasional pains in her ankle.

Four blood cultures were made, all of them on days when there was no pyrexia. The first, done on 21st July, yielded no growth. The second, on 5th August, when the erythematous rash was present yielded a gram-negative diplococcus. The third, on 8th August, again yielded a gram-negative diplococcus which was proved culturally and biochemically to be a meningococcus; no typing sera could be obtained at that time. The fourth, on 19th August, after subsidence of the pyrexia, yielded no growth.

The spleen was not enlarged. On 8th August a roughened pulmonary second sound was heard. There was never any sign of meningitis, and lumbar puncture on 29th July yielded a clear fluid, under no increase of pressure, and normal to all tests. There was never any definite leucocytosis in the blood, four counts being 7600, 8600, 6400 and 7600 per c.mm. Gonococcal complement fixation test on 8th August was negative. Two specimens of urine were negative by bacteriological examination. A throat and a nose swab examined for meningococci on 4th September were negative.

A vaccine was prepared from the patient's own meningococcus and administered during September and after transfer from hospital with the object of increasing her immunity against the organism and so preventing the onset of meningitis. The patient left the Convalescent House at the end of October and returned to work; there was no recurrence.

This case was, then, one in which the joint infections were predominant. The skin lesions, though typical, occurred only in three crops. The pyrexia, though intermittent, was irregularly so, and only " malaria-like " for a week or so in August. Apart from her joint condition she never felt really ill except perhaps in the higher pyrexial periods of late July and early August. The patient was off work for over five months. Although she had been living in a one-roomed house with her father, mother, three brothers and two sisters, she apparently did not convey the infection to any of the others.

CASE 2.—J. H., aged 16, farm worker. Admitted on 7th October 1941 to the Royal Infirmary in the care of the late Professor W. T. Ritchie, who kindly furnished the details of the case. For six weeks previously she had been having attacks in which she had shivering and was " fevered up." These would last a day and then she was all right. She was off and on work for the first month, and then went off work. Four days before admission her temperature was 101°, and the next two days normal. The day before admission it was again up to 101°.

On admission the temperature was normal. There was nothing to be found to indicate the cause of the pyrexia. On 9th October, three days after the last pyrexia, the temperature shot up to 103·6° and was down the following morning. To continue with the story of the pyrexia, the temperature remained normal till the 13th when it rose to 100·2°, was normal on 14th, 15th and 16th, and rose to 102·4° on the 17th. It was again normal till the 21st when it rose to 102·4°. It will be noticed that though the temperature was " malaria-like," the first two recorded remissions were three-day type, the last three four-day type. In the meantime numerous investigations had been in progress, Widal tests, Weil-Felix tests, sheep cell agglutination test, examinations for leptospiræ and malarial parasites, and urine examinations; these were all negative. Lumbar puncture on 22nd October yielded a normal fluid. It had been found that there was a polymorph leucocytosis varying from 6800 and 7400 per c.mm. in apyrexial intervals to 16,600 and 16,800 during attacks. A blood culture had been taken on 13th October, and this after eight

days' incubation yielded a growth of meningococcus, proved by cultural and biochemical reactions. It was not agglutinable by Group I and II sera. A second blood culture taken on 22nd October gave a negative result. The patient was transferred on that day to the Fever hospital, where under sulphonamide treatment she made rapid recovery without further attacks.

This case is interesting because apart from the intermittent pyrexial attacks there were no symptoms. There were no pains, no articular involvement, no skin lesions, and she felt well between attacks. During the first month of illness she was for the most part ambulatory. This is the type of case which in malarial countries is treated for a varying length of time with anti-malarials.

CASE 3.—A. T., aged 19, miner. Admitted on 28th October 1942 to the Royal Infirmary in the care of Professor Stanley Davidson, who has kindly supplied the clinical details. The illness began a fortnight before admission with a sudden shiver, after which he felt feverish and weak but continued work for two days. He had one attack of nausea and vomiting, and continuous frontal headache. On the third day he had another shivering attack and went to bed. He felt feverish and perspired profusely. About this time he began to have pain in the wrist joints without redness or swelling; the pain disappeared after two days. He next had similar transient pain in his elbows, and, after a week's illness, in his knees. At the same time he noticed some bright red nodules, first around his wrists, then on his arms, and last on his chest and legs. They came out in crops, fading in a few days. The largest nodules were slightly tender; the others caused no discomfort. The patient's condition had improved before admission, and he felt a little stronger and less feverish. He coughed now and then, bringing up whitish sputum. His appetite was poor and he was constipated. There was no sore throat. The frontal headache was continuous for over a week, but had disappeared before admission. He was sent to hospital with a diagnosis of acute rheumatism.

On admission he was put on salicylates, which produced no improvement. It was noted that his papular rash was not sufficiently deep seated or indurated to be that of erythema nodosum. His temperature was of intermittent type, with a rise on the first four evenings in hospital to 99·6°, 99·8°, 102·6° and 102° respectively. There was no rise on the fifth day, but on the sixth it again reached 102°. Blood culture was made on 31st October, the third day in hospital, when the temperature was rising, and this yielded in twenty-four hours Gram-negative diplococci resembling meningococci. The sugar reactions were not at first typical, but ultimately it fermented both glucose and maltose. In other respects it was a typical meningococcus, but it was not typed serologically. A second blood culture made on 2nd November again yielded the meningococcus, this time after three days' incubation. His temperature was rising towards 102° when the blood was taken. Widal and Paul-Bunnell tests had been negative, as had electro-cardiographic examination. Cytological, chemical and bacteriological examinations of cerebrospinal fluid taken on 2nd November also gave negative results, and a throat swab did not yield the meningococcus. There was no neck rigidity and no Kernig. On 30th October the white cells of the blood were 11,800 per c.mm., with 77 per cent. polymorphs; on 2nd November they were 16,400. On both of these days there was pyrexia. On 9th November, after the temperature had fallen, the white cells numbered 8000 per c.mm.

Salicylates were stopped when the result of the blood culture was known and

sulphadiazine treatment begun. He was given 7 grammes on 2nd November, 6 grammes on each of the three following days, and a final dose of 3 grammes on 6th November. The temperature fell to normal within twenty-four hours of the first dose and remained so, save for a slight rise before discharge due to vaccination against small-pox. Joint symptoms disappeared almost at once, and the skin lesions faded. A third blood culture made on 9th November yielded no growth. He was discharged cured on 17th November.

This, then, was a fairly typical case, cut short by relatively early diagnosis and sulphadiazine treatment. The pyrexia was apparently mainly of quotidian type. The first diagnosis was acute rheumatism, but there had been no effusion into the joints before chemotherapy was begun.

The blood cultures in these 3 cases were made primarily in fluid media, usually ordinary and trypsin broth, with no enrichment save the blood of the patient.

Part II. Clinical Review

Clinical Condition

This review covers 259 published cases and the 3 just described, but in some, especially in the later epidemic series, full clinical details are lacking. The total number of cases analysed therefore differs in various sections according to the details available.

The *mode of onset* was often abrupt, with headache, shivering, pyrexia and occasionally vomiting. Many of the cases were described as aching all over. There was usually sweating as the pyrexia subsided. This first attack was frequently thought to be influenza. Fifty-seven out of 251 cases had sore or inflamed throat immediately before the illness, or during the first few days: that is, 22 per cent. Two series of cases in epidemic periods account for 37 of the 57. But in other epidemic series there was no initial sore throat. In the sporadic cases it was exceptional for the illness to begin with sore throat. In some cases the headache was more intense, and when combined with vomiting caused a suspicion of meningitis.

In other cases the primary pyrexia was accompanied by the typical papulo-nodular skin eruption, and the pains were definitely localised in the joints, while redness and tenderness of joints were also sometimes present from the beginning.

In many cases the onset was more insidious, and sometimes the patient was not seen by a doctor for some weeks from the beginning of the illness. Many cases were ambulant at first, except in the pyrexial periods.

The *shivering* or *chill* was as a rule not so marked as that of malaria, and in a fair number of cases was not observed at all. In some it was a definite rigor with chattering of the teeth, and in some

cases "shaking chills" were the chief complaint of the patient. In one case (Monziols and Loiseleur, 1910) the shivering began as a trembling in the left hand, then of the right, and finally of the upper limbs' and thorax with the rest of the body remaining motionless; but perhaps there was a hysterical element in this case.

The *headache* varied in intensity, but never seemed to be so intense as what has been described as the "bursting headache" of meningitis. *Vomiting*, occasionally noted at the onset, occurred only rarely as the illness progressed. It was difficult to assess the incidence of *sweating*. In some cases it was always present with the subsidence of the pyrexia, sometimes described as "drenching," but there was no note of it in a number of cases. As with the shivering it was definitely less characteristic of meningococcæmia than of malaria.

Enlargement of the spleen was observed in 20 out of 250 cases; that is, in 8 per cent. It was usually just palpable in these cases; a tender or greatly enlarged spleen was only observed when there were complications such as endocarditis with congestion or infarctions, or, as in 2 cases, something in the nature of Banti's disease.

A *polymorph leucocytosis* was so common as to be of diagnostic importance. A relative mononuclear increase was described in two early French cases, but in no others. Some cases showed little or no polymorph increase at one stage of the illness, and a definite increase at another. The increase was usually greater during a pyrexial period. In most cases the leucocytes numbered between 10,000 and 20,000 per cubic millimetre, but, in some, counts of 30,000 and over 40,000 were made. Polymorphs commonly constituted about 80 per cent.

A disproportionately slow pulse was mentioned in a few cases.

Cases which were *ambulant* in the earlier stages of the illness were fairly common; in them the pyrexial periods were usually separated by a few days of good health. But even cases with a daily rise of temperature were sometimes partly ambulant. It was curious that at least two of the ambulatory cases were found to have endocarditis, and died. Hennell and Wiener's (1930) case, for example, went to work each morning for three weeks, but had to go to bed each afternoon with chill, high fever and drenching sweat. He was sometimes able to work in the evenings. He ultimately died after showing clinical evidence of endocarditis. Most of the ambulant cases, however, were definitely quite fit during apyrexial intervals. In the pyrexial period there was anorexia, and sometimes nausea, while in the interval there was often very good appetite, described in one French case as "ferocious," and a marked sense of well-being.

In *uncomplicated* cases the patient usually remained surprisingly well, even after long illness, but in a few there was increasing anæmia and weakness, sometimes with loss of appetite. It is evident from the histories that such symptoms should arouse suspicion of complications having taken place, but in some cases, apparently uncomplicated, the patient became progressively more ill, till a terminal meningitis

occurred.   As will be shown later, however, death did not take place in any case without some complication such as meningitis or endocarditis, having first occurred.

The *duration of the illness* varied in this series from a few days to two years and four months.   The shortest case with definite intermittent pyrexia was Professor Friedemann (Friedemann and Deicher, 1926), who was infected by being coughed over by a patient with meningococcæmia during a clinical lecture.   The illness lasted five days.   The case of longest duration was a soldier of the British Army of Occupation in Germany (Kennedy, 1926), whose illness began in Cologne in December 1923 and ended fatally in Britain in April 1926. A diagnosis of endocarditis was made by more than one physician, but no heart lesion was found post-mortem.   A case with what may have been recurrences over a period of years was described by Heinle (1939).   She had two proved attacks separated by an interval of eighteen months of comparatively good health, and had had four previous illnesses, clinically of a similar nature, at three-year intervals during the preceding twelve years.   Meningococci were obtained from the nose and throat of this patient, so she may have been a chronic carrier, with occasional invasions of the blood stream.

The *age incidence* extended from eight months to fifty-nine years. Thirty-two cases were below the age of eighteen, 17 of them below twelve, and 9 below six.   The majority were between eighteen and thirty-five, the numbers in this period being swelled by epidemics among troops.   The incidence among males was increased for the same reason.   It is evident that the condition is rare in the elderly and old.

The complications met with were meningitis, endocarditis, pericarditis, myocarditis, pneumonia, empyema, eye infections, nephritis, epididymitis, orchitis, sinusitis, parotitis, and jaundice ;   and these, like the type of pyrexia, and skin and joint lesions are discussed in the following sections.

TYPE OF PYREXIA

The temperature was definitely intermittent for at least part of the illness in 164 out of 200 cases ; that is, in 82 per cent.   In some cases it was described as " septic " or " irregular."   In a few it was described as remittent, but in more than one of these the published chart showed it to be intermittent.   In 3 cases it was " typhoid-like," but in one of these it became intermittent later.   In many cases it was remittent or irregular for part of the illness, with one or more periods of fairly regular intermittency.   In other cases periods of continued temperature occurred, preceding or following periods of intermittency.   The occurrence of complications such as meningitis, endocarditis, or arthritis naturally altered the pyrexial pattern.

The cases with intermittent pyrexia showed three main types : the quotidian, the tertian (every second day) and the quartan (every

third day). The quotidian type was often very regular, the rise being in the afternoon or evening. The tertian type usually only continued for three or four rises and then there might be a quartan rise, and the converse was also true. Fourth day pyrexial periods were occasionally seen, but longer regular intervals were rare. There were, however, cases such as that described by Martin and Dansie (1944), in which there were widely separated pyrexial periods ; in their case only 3 in six weeks, although there were almost daily crops of spots. He was a soldier and was kept under constant observation ; ordinarily such a case would be ambulant, and perhaps attending a skin department. There was no case in which the intermittency continued to be regular over as long a period as in a typical single-infection case of untreated malaria, but the periodicity was sufficiently malaria-like to cause fairly numerous cases to be treated as such for long periods.

SKIN LESIONS

Labial herpes is more common in cerebrospinal fever than rashes and other skin lesions, but the reverse is true in chronic meningococcæmia. The incidence of either type of lesion varies very much in different epidemics of meningitis.

Herpes was present in only about 3 per cent. of the cases of meningococcæmia, and usually only in a meningitic phase. Two cases showed herpes in the absence of cerebrospinal involvement. In a third case there was corneal as well as labial herpes, and in another both labial and intercostal herpes, but there was meningitis at the time in both. Making allowance for the possibility of its presence sometimes being missed, herpes is much less common in meningococcæmia than in meningitis.

Skin rashes in cerebrospinal meningitis are usually of hæmorrhagic type, usually either with petechial or larger purpuric lesions. In sporadic cases the incidence is low. Marked purpura with coalescing lesions is usually associated with fulminating infection, with or without meningitis.

Rashes or other skin lesions, excluding herpes, were present in 213 of 248 cases of meningococcæmia ; that is, in 86 per cent. Sparse skin lesions may have been missed in a few of the 35 negative cases, but in most of them such signs were specifically looked for. In some there was a long stay in hospital.

The skin lesions of meningococcæmia have been described many times, from Salomon (1902) onwards, usually in a description of an individual case, sometimes, as by Appelbaum (1937) and Stott and Copeman (1940), in a study of a series of cases. The eruption usually appeared within a few days of the beginning of illness, but sometimes its occurrence was delayed. It was most commonly seen on the arms and legs, hands and feet, and the back, and less commonly on the abdomen and chest. The face was affected in only a few cases. The

eruption tended to appear in crops at the same time as the rises in temperature so that fresh and fading lesions were to be seen at one time. Macules, papules, nodules, and, less commonly, petechiæ were described. The typical lesion was the tender nodule, resembling the condition known as *erythema nodosum*, and this was to be seen in all stages of reddish spot, papule, and nodule varying in size from a few millimetres to 2 cm. They sometimes attained a larger size, resembling blind boils. The nodules were usually tender and sometimes painful. They sometimes became purulent. Petechiæ were also frequent but less so than the papular lesion, and a pinhead sized hæmorrhage surrounded by a macular areola was described by Appelbaum and others. Sometimes the rash was purely petechial. The character of the eruption sometimes varied at different periods of the illness, and a petechial rash was often seen when a terminal meningitis occurred. Petechiæ suppurated in a few cases, and the larger petechial areas sometimes sloughed. The macular lesions were usually rose pink at first, then red, and became brown as they aged. The macules were described by some authors as fading on pressure, by others as not fading on pressure. Roseolar spots were the main lesions in a few cases. They were usually larger than those of typhoid, but in one case the roseolar spots and type of fever led at first to a diagnosis of typhoid. There was a scarlatiniform rash in one case, and measly rashes in 5. In some cases erythema was most marked in the neighbourhood of the joints. Itching was mentioned in only 2 cases.

JOINTS

It was not always easy to distinguish pain in joints from pain in bones and muscles. In some cases the pains in meningococcæmia were described as " diffuse," or as " generalised pains in back and limbs." Occasionally there were pains in muscles or bones without pains in the joints ; in the case of Roger and Poursines (1932) for example the pains were definitely in the bones. In the great majority of cases however in which there was pain in the limbs it became localised in the joints. Pain in the joints was specifically mentioned in 154 out of 236 cases in which full clinical details were available ; that is, in 65 per cent. Rolleston suggests that pains in the joints in epidemic meningitis are " very probably due to meningococcic emboli and hæmorrhages in the synovial membranes of the joint." If this be the case then the figure of 65 would represent approximately the percentage of cases in which joint infection took place in the present series.

If one takes swelling or tenderness of joints as definite evidence of inflammation, or arthritis, this evidence was present in 56 of 236 cases, or 24 per cent. In 22 of these there was definitely fluid in a joint or joints, that is, in 9 per cent., while in 5 of the 20 the fluid was shown to be purulent ; that is, in 2 per cent. of 236 cases. The figure of 24 per cent. of joint infections seems to be considerably higher than

that met with in cerebrospinal meningitis, as one would expect from the prolonged or recurrent bacteræmia in these cases. Herrick and Parkhurst reviewed the literature of joint infection in cerebrospinal meningitis in 1919, and Schein again in 1938. The former found articular involvement in 6·5 per cent. of Herrick's series of 902 cases of cerebrospinal meningitis. Sainton (1919) alone, and in collaboration with Maille and with Bosquet, gave 20 per cent. as his figure. He thought it often passed unobserved. This is a much higher figure than that given by most writers. It is difficult sometimes to distinguish joint infection from serum sickness. Various classifications of the joint infections have been suggested by these writers.

Pain in the joints in the present series was usually not very severe but there were exceptions. One case had effusion in many joints, with " agonizing " pain, and tenderness to touch was very marked in some cases.

In the five cases in which there was proved suppurative arthritis, the joints affected were, respectively, wrist and knee joint ; right shoulder, right knee and left wrist ; left hip ; elbows and knees ; left knee and a right metacarpo-phalangeal joint. Meningococci were obtained from the joints from the first, second, fourth, and fifth cases. There was complete recovery without after effect in the first case ; the second died of meningitis (Sainton and Bosquet, 1917). Ankylosis of the joint followed in the third case (Brodin, Marquézy and Wolf, 1923). The fourth case (Gardiner, 1928) was one with general sepsis including irido-choroiditis, suppurating skin lesions and bronchopneumonia. There was complete recovery from the joint infections. The fifth case (Heinle, 1939) was extremely septic, with large subcutaneous abscesses, yielding as much as 70 c.c. of meningococcal pus. There was complete recovery from the joint infections, without after effect, save for a destructive lesion of the second right metacarpo-phalangeal joint as shown by X-ray. No other cases with fluid in the joints had after effects, so there were in all only two of the 236 cases with permanent ill results from joint infection.

In addition to cases of cerebrospinal meningitis, and of meningococcæmia, in which there is articular involvement, cases of meningococcic arthritis occurring as an isolated phenomenon may be met with. Three were described by Sainton (1919), but the first two had a measly rash, and it may be that one of them was the case of Sainton and Bosquet (1917) to which reference has already been made. These two cases would more properly be described as meningococcæmia. The third case had a purulent arthritis with no other symptoms save pyrexia. Campbell and Greenfield (1936) observed a similar case, in a coloured boy of fifteen months, the joint affected being the knee. Meningococci were obtained from all these cases, and there was complete recovery except possibly in the last, in which the ultimate outcome was not known. In such cases there is early localisation in the joints and the clinical picture of meningococcæmia does not appear.

Endocarditis.—The incidence of this important complication was very difficult to assess. If only those cases are accepted as endocarditis which were proved by post-mortem examination, or by such evidence as infarctions, the mortality rate in meningococcal endocarditis would be very high. But there were cases which recovered after a varying amount of clinical evidence of endocarditis, and if these were included the rate would be much reduced. Some cases of endocarditis appeared to have the infection localised in the endocardium from the beginning, and the clinical picture typical of meningococcæmia did not appear. Further, it was necessary for comparison to include endocarditis occurring in the course of cerebrospinal meningitis. For these reasons endocarditis has been considered separately and has been discussed in a separate paper (1945).

Myocarditis.—The incidence of myocarditis in meningococcæmia was also difficult to establish. There was evidently a toxic process in some cases, but evidence of invasion of the myocardium by meningococci was scanty. In over 260 cases myocarditis was mentioned five times : in under 2 per cent. Svestka's (1915) case was found post-mortem to have parenchymatous and fatty degeneration of the myocardium. Stevenson's (1931) case had post-mortem, in addition to endocarditis, minute abscesses in the muscle wall containing meningococci. This patient was saturated with meningococci at the time of death. Stewart-Wallace's (1936) third patient showed moderate parenchymatous degeneration of the myocardium post-mortem. Appelbaum (1937) diagnosed myocarditis in a female patient who recovered, and Monziols and Loiseleur (1910) had a patient who recovered from meningococcæmia with empyema, but still showed signs of myocarditis.

Saphir (1936) reported the post-mortem examination of two cases of meningococcal meningitis in which there was acute myocarditis with meningococci in the inflammatory lesions. Worster-Drought and Kennedy (1917) had a case of meningococcus ulcerative endocarditis with, post-mortem, acute and widespread myocarditis.

Pericarditis.—Pericarditis was a rare complication in the series of over 260 cases of meningococcæmia. It was found in two cases, or less than 1 per cent. It was the cause of death in Marshall Findlay's (1919) case in which there was also parotitis. The meningococcus was obtained post-mortem from the pericardial exudate. In Cecil and Soper's (1911) case of endocarditis, fibrous adhesions in the pericardium were found post-mortem.

Orgain and Poston (1939) described an unusual case of meningococcal pericarditis, without any of the usual features of chronic meningococcæmia. Meningococci were obtained by pericardial puncture. He recovered with sulphanilamide and serum therapy.

Pulmonary Infections.—Jacobitz (1907) described a case of meningococcus pneumonia without meningitis ; 4 cases of bronchial catarrh with intracellular gram-negative diplococci, from 2 of which meningococci were obtained ; and 4 cases of pneumonia, 3 lobar and

1 lobular, with meningitis, with sputum yielding growths of meningo-coccus from all four.   These were proved serologically, the titres being extremely high, from 1 : 500 to 1 : 2000.   A good deal of scepticism was expressed about these findings, but in 1919 Fletcher obtained similar results, showing that epidemics of meningococcal pulmonary infection do occur.   He made cultures after death from the lungs and heart blood of 36 American soldiers who had been taken ill with symptoms of influenza on board transports crossing the Atlantic, and had died from broncho-pneumonia.   In some of them the only organisms seen in films from the lungs were gram-negative diplococci in enormous numbers, chiefly polymorphs.   Meningococci were cultured from the lungs of 11 of the 36 cases ; and in three instances from the heart blood as well.   Of 7 strains typed, 6 were Type 2, the seventh Type 1. In all these 11 cases *B. pfeifferi* was also obtained.   There was no evidence of meningitis clinically or at post-mortem examination in any of these cases.   This is presumably an example of an epidemic of influenza in a closed community, with secondary infection by meningococci from carriers, the localisation of the meningococcal infection in the lungs being due to initial damage by the organisms of influenza.

Meningococci are also occasionally found in nearly pure culture in the sputum of sporadic cases of bronchitis as in the case described by Galloway and Wallace (1932), but in a few other cases of this kind examined by the writer the organisms have usually been other Neisseria of *M. catarrhalis* or *pharyngis siccus* type.

In the series of 262 cases of meningococcæmia under review pulmonary infection due to the meningococcus was very rare.

Monziols and Loiseleur (1910) described a case of meningo-coccæmia with pneumonia and empyema.   Meningococci were obtained in films and by culture from the empyema fluid.   Herrick (1919) had a fatal case with bronchopneumonia and sinus infection. Meningococci were obtained from the sphenoidal sinus, but not, apparently, from the sputum   He had another case complicated by bronchopneumonia and empyema, and measles ; meningococci were obtained from the empyema pus.   Gardiner's (1928) case with irido-choroiditis had bronchopneumonia in the course of the illness, not proved to be meningococcal.   In a few other cases there were pulmonary complications shown to be due to other organisms such as Type 1 pneumococcus.

Infections of the Eye.—Iridocyclitis occurred in 3 cases : that is, in a little over 1 per cent.   In Bovaird's case (1909) conjunctivitis developed into panophthalmitis.   The eye was preserved but with loss of vision.   The eye was enucleated in Bittorf's (1915) case because of hæmorrhage into it.   In Gardiner's (1928) patient, a girl of two-and-a-half years with suppurating joints, there was double iridochoroiditis with loss of sight.   Conjunctivitis was mentioned in another case, and corneal ulcer was encountered once.   One case had corneal herpes.

Nephritis.—Of 236 cases of meningococcæmia under review there were 13 with nephritis, including only those proved post-mortem or showing definite casts in the urine. There were other cases with small amounts of albumen and red blood cells in the urine, sometimes the result of sulphonamide treatment. Of the 13, 4 had endocarditis, with, in 3 of them, infarctions, so that the nephritis cannot be assumed to be the result of a pure meningococcæmia. In the fourth case with endocarditis there was chronic nephritis, which may possibly have been connected with the long-standing ·meningococcal infection. Of the remaining 9 cases there was in one " extensive renal damage . . . before the onset of the· *Neisseria intracellularis* infection." This leaves eight instances of nephritis, or pyelo-nephritis occurring in the course of meningococcæmia : 3 per cent. The meningococcus was not found in the urine of any of them, but as a rule no special search was made. Two died and six recovered.

Epididymitis and Orchitis.—In 236 cases of meningococcæmia, orchitis occurred only once, and epididymitis five times ; taken together, in 6 cases, or 2·5 per cent. The case in which orchitis occurred was fatal, nephritis being the probable cause of death. In 5 of the cases with epididymitis it was a minor complication, but in the sixth case, described by Laird (1944), bilateral epididymitis was the primary condition, and the other features of meningococcæmia developed later. This case was however, not bacteriologically proved, and may have been gonococcal.

Infection of Sinuses.—In 262 cases of meningococcæmia, proof of sinus infection was to be found in only 3, or 1 per cent. One of Herrick's (1919) cases had infection of the right maxillary antrum, not examined bacteriologically. Another patient, also Herrick's, who died of bronchopneumonia, was˙found post-mortem to have abscesses of the sphenoidal and left frontal sinuses, and anterior and posterior ethmoidal cells. Meningococci were obtained from the sphenoidal sinus. A case of Friedemann and Deicher (1926) showed meningococci in the secretion from the maxillary antrum.

In the majority of cases there was no record of examinations specially directed to detect sinusitis. It is evident, however, that only a small percentage had symptoms suggestive of sinus infection. In 4 cases X-ray examination showed no abnormality of the sinuses, and in other 3 negative bacteriological examinations were made. In one of these sinus lavage yielded pneumococci.

Parotitis occurred in 2 cases, in one of which there was also pericarditis (Marshall Findlay, 1919).

Jaundice.—Jaundice occurred in 7 or a little under 3 per cent. of the cases of meningococcæmia, but it was difficult to determine whether there was any connection between the meningococcal infection and the jaundice. In the ship epidemic of combined influenza and meningococcal infection, chiefly affecting the lungs, described by Fletcher (1919), there was one patient whose skin was bright yellow for

several days before he died.   Type 2 meningococcus was obtained from his heart blood and lungs.   Railliet and Ginsbourg (1930) described a fatal case in which meningococcæmia and agranulocytosis followed what was described as epidemic jaundice.   This was a very atypical case, and the authors did not themselves suggest that the period of jaundice was part of the meningococcal infection, but it is conceivable, in view of the final case to be described, that it was.   Weindel's (1934) case of meningococcal endocarditis developed general jaundice, but this was terminal, with enlargement of the liver and spleen and myocardial degeneration.   Three other cases showed slight jaundice in the course of their illness.

Finally, a case of jaundice definitely regarded by the physician as due to Type 1 meningococcus has been reported by Crawford (1944). He had shivering, vomiting of blood-streaked material, with early jaundice, severe headache, a rash at first macular, later purpuric, and a polymorph leucocytosis.   Tests for leptospiræ were negative.   At the end of ten days he was extremely ill and severely jaundiced.   Sulpha-thiazole was tried tentatively with immediate improvement, and the recovery of Type 1 meningococcus from the blood after seven days' incubation finally established the diagnosis.   There is the possibility of a double infection here, but the immediate effect of sulphathiazole is corroborative of a pure meningococcus infection.

The mechanism of the production of severe jaundice by an organism so susceptible to acid gastric juice and bile as the meningococcus is not clear, but the last case seems to prove that it can be so produced.

DIAGNOSIS

Various points have already been discussed in the section " clinical condition."   In typical cases perhaps the most important diagnostic feature was the skin lesions of erythema nodosum type coming out in crops with the recurrences of pyrexia, but in many cases these lesions were not numerous, and they were irregular in their time of appearance. The intermittency of pyrexia was helpful, but the joint affections were often misleading.   It is also obviously much more difficult to get a clear picture of such cases in their own homes than when they are under constant observation in hospital.

In a large proportion of the sporadic cases diagnosis was made more or less fortuitously by blood culture, or by development of meningococcal meningitis.   It might be expected that typical cases with the syndrome intermittent pyrexia, skin lesions and arthralgias, and a polymorph leucocytosis in the blood, would frequently be diagnosed on clinical grounds, but in many the cause was unsuspected before the production of bacteriological proof.   With a more widespread knowledge of the condition the proportion diagnosed before the meningococcus was obtained was increased.   In periods of epidemic meningitis, as sometimes during the recent war, cases coming to a ward

were often suspected or diagnosed before bacteriological proof was available, but in nearly all of these the primary diagnosis had been different.

In less typical cases it was impossible to arrive at a clinical diagnosis on clinical grounds only. Such cases were usually diagnosed by positive blood culture, but, as will be shown in the third paper, repeated cultures were sometimes necessary. Even where full facilities for blood culture are available such cases may be missed.

The intermittency of the pyrexia frequently led in malarial districts to a diagnosis of malaria, and treatment with quinine was common. The ineffectiveness of the drug along with the absence of the parasite from the blood and the presence of a polymorph leucocytosis showed the diagnosis to be wrong. In some cases this evidence was afforded by the onset of meningitis.

In other cases the pains and swellings of joints led to diagnoses such as rheumatic fever and subacute rheumatism, and myalgia was a common early diagnosis in service cases. Tenderness of the shins caused some cases to be regarded as trench fever. Diagnosis of erythema nodosum was not uncommon, measles was diagnosed a few times, and chickenpox at least once. Differentiation from Malta or abortus fever was usually made by negative agglutination tests, and Widal tests were carried out in a large number of cases. Rat-bite fever was sometimes suspected. Influenza was, of course, a common diagnosis in the first few days of illness.

Agglutination and complement fixation tests with the patient's serum were used with a certain amount of success in some cases. Isolation of the organism from skin nodules was achieved in a few. These tests are discussed in the third paper.

INCIDENCE OF MENINGITIS IN MENINGOCOCCÆMIA

Of 262 cases of meningococcæmia, 192 had no meningeal involvement. The proportion of cases without such involvement has greatly increased in recent years owing to the cutting short of the illness by sulphonamide treatment. Of the 70 meningitic cases there were 53 in which the meninges were infected in from a few days to two years after the beginning of the meningococcæmia. The other 17 were cases of primary meningitis in which meningococcæmia set in after recovery from meningitis. In 5 of these there was a recurrence of meningitis at some time in the meningococcæmic phase, and in other two there were repeated rather mild attacks of meningitis in the meningococcæmic period.

In the group of 53 cases in which meningococcæmia preceded meningitis, 4 developed meningitis in the first week of illness, 4 in the second week, 1 in the third week, and 4 in the fourth week; that is, 13 in the first month; 16 in the second month, 8 in the third month, 2 in the fourth month, 4 in the fifth month, 1 each in the seventh, eighth, tenth and eleventh months, and 1 after two years. In 5, meningitis developed at undetermined periods " late " in the illness.

MORTALITY: RELATION TO MENINGITIS AND OTHER COMPLICATIONS

Twenty-six of the total 262 cases were fatal : that is, 10 per cent. An analysis of the cases gives the following results :—

Ameningitic Cases.—There were 192 cases with 9 deaths, or a mortality of 4·7 per cent. Ninety-two of the cases occurred in the pre-sulphonamide period, including in this category one which had some sulphonamide treatment late in the illness, and 9 of these died : a 10 per cent. mortality. One hundred cases had sulphonamide treatment and none of them died.

The fatal cases were 4 diagnosed clinically as endocarditis, one with pericarditis, one with sinusitis and bronchopneumonia, one with nephritis, and one with agranulocytosis ; in the ninth case there was a " sudden unexpected death."

We have therefore the striking result that, excepting the unexplained death, there was no death in any case of uncomplicated meningococcæmia. The absurdity of the statement of some of the earlier writers that the onset of meningitis in meningococcæmia improves the prognosis is manifest. Except in the rare cases in which it affects the heart, lungs, and possibly the kidneys, and those cases in which it affects the brain, the meningococcus can reside for long periods in the body with intermittent invasions of the blood stream without fatal result, and often with relatively little disturbance. There is little evidence of toxæmia in many such cases.

Cases in which Meningococcæmia was followed by Meningitis.— This group of 53 cases furnished the greater number of fatal results. There were 16 deaths, a mortality of 30 per cent. Only 5 of this group were treated with sulphonamides, all in the meningitic phase and all with recovery, most of the cases occurring before sulphonamides came into use. The scarcity in recent years of cases in which meningitis supervened on meningococcæmia is due chiefly to abortion of the infection by sulphonamides, but also perhaps to some extent because cases in epidemic series were withdrawn by writers from the category of meningococcæmia, and placed in the meningitic group, if cerebral involvement took place.

An analysis of the 15 fatal cases shows that meningitis was complicated by endocarditis in 3, and possibly in a fourth In one of the endocarditis cases, and in the suspected endocarditis case, there was also nephritis ; and there was nephritis in another fatal case. One case died of anaphylactic shock ; the meningitis in this case was mild. The cerebral invasion supervened after periods varying from a week to two years. No serum treatment was given in 7 of the cases, and in nearly all the others it was only given near the end of the illness after terminal meningitis had set in.

Cases in which Meningococcæmia followed Meningitis.—Seventeen cases fall into this category, including 2 in which the time of onset of meningitis is doubtful. In 2 cases there were repeated attacks of meningitis, apparently mild, in the course of the illness. In 5

others there was a second attack of meningitis during the course of the meningococcæmia, while in 10 meningococcæmia followed a primary meningitis without any recurrence of meningitis.

In most of these cases the patient was regarded as convalescent or cured when meningococcæmia set in. All symptoms had disappeared and the cerebrospinal fluid was clear for a period usually of a few days or a week or so before intermittent pyrexia and skin lesions made their appearance, but in one case there was an interval of about three months with apparently good health, between recovery from meningitis and commencement of meningococcæmia. It does not seem to have been proved that the meningococcus was of the same type in the two attacks.

· Only 2 cases of the 17 were fatal : under 12 per cent. One reason for this contrast with the mortality of the pre-meningitic cases is quite definite. The nature of these cases was recognised from the beginning and practically all were given vigorous serum treatment at the beginning of their illness, and this serum therapy was reinstituted with the recurrence. Another is that 10 of the cases had made a complete recovery from meningitis and were now cases of uncomplicated meningococcæmia. The two deaths were a case in which myocarditis was found post-mortem, and another in which after apparent recovery from meningococcal meningitis complicated by Type 1 pneumococcal pneumonia, there was almost immediately a recurrence of meningitis and meningococcæmia with hæmorrhagic eruption and periarticular inflammation ; he died in spite of active serum treatment. It is a little doubtful if this case should be admitted to the category of meningococcæmia, as it is not certain that there was ever a completely ameningitic phase.

Two of the cases were treated with sulphonamides during the meningococcæmic phase and both recovered.

TREATMENT

Little need be said of methods of treatment used before sulphonamides came into use. The most important was of course serum therapy. It is not worth while attempting to analyse the effects of serum treatment as the number of varying factors is too great ; the nature of the complications, the stage when treatment was begun, the type of infecting organism, the potency of the serum available and its specificity for the infecting organism, the dosage and route of administration and so on. Many physicians were definitely of opinion that serum had been of value, sometimes of great value, and this seemed specially so of Group I cases, the serum for which is more effective than that available against Group II and other strains. Nevertheless the French physicians tended after the 1914-1918 war to try other forms of treatment, and fixation abscess, protein shock by injections of milk, sterile pus and intravenous vaccines, chemotherapy by intravenous injection of acriflavine, trypaflavine, optochin and arsenobenzol were used and good results claimed for all. Other observers found that the application of each remedy in turn led to improvement

which was only temporary. It is difficult to assess the value of treatment in a condition which tends to show sudden spontaneous recovery. Quinine was frequently given on the assumption that the case was malarial, and salicylates when the primary diagnosis was rheumatism, but both were usually found to be ineffective.

In five cases anaphylactic shock during serum treatment was immediately followed by recovery from meningococcæmia, but in a sixth case death took place during shock.

The sulphonamides used were sulphanilamide, sulphapyridine and sulphadiazine, and of their complete efficacy there was no doubt. One hundred and seven cases were adequately treated with sulphonamides and there was recovery, usually rapid, in all. In 100 of the cases treatment was begun in the pure meningococcæmic phase, and there was no development of meningitis or other serious complication in any. In two the illness began with meningitis, apparently cured by serum in one of them. The ensuing meningococcæmic phase was cured in each case with sulphonamide. In five, sulphonamides were begun in a meningitic phase following meningococcæmia. One patient was given some sulphonamide too late in the illness to be efficacious.

A typical course of sulphonamide therapy was described in the record of Case 3, in the care of Professor Stanley Davidson, but some cases required more prolonged treatment. Sulphadiazine was the form most commonly used in the series under review.

INCIDENCE OF MENINGOCOCCÆMIA

It is evident that the number of ameningitic meningococcal infections is much larger than is suspected. Many cases diagnosed as, for example, acute and subacute rheumatism, or in the Army, myalgia, may have been meningococcal. Probably every physician can remember also cases of obscure pyrexia which may have been of this nature, cases in which only *repeated* blood cultures might have revealed the cause of the condition. Even cases showing only skin lesions of the erythema nodosum type may be meningococcal. The patient of Martin and Dansie (1944), to whom reference has already been made, was only diagnosed because he was a soldier and, though feeling perfectly well, was kept in bed under observation. In civil life such a case would have remained undiagnosed, as he would not have been observed during his brief and rare rises of temperature, and a positive blood culture would not have been made.

Probably in the future, cases suspected of being, or diagnosed as, meningococcæmia will be put on sulphonamides at an early stage and the long chronic type of illness may no longer be seen, unless drug-resistant types of meningococci are evolved.

Since the above was written (in 1944) penicillin has also become available for such cases.

[To be continued]

NEW BOOKS

Cancer of the Scrotum in Relation to Occupation. By S. A. HENRY, M.A., M.D., F.R.C.P., D.P.H. Pp. viii+112, with 30 figures. London: Oxford University Press. 1946. Price 15s.

The material contained in this book formed the basis of the Hunterian Lecture delivered by the author in 1940. It consists of a detailed study of 1355 cases notified subsequent to 1920. The incidence of the disease in various occupations is studied and there is an account of the various carcinogenic agents which give rise to the condition. An interesting section shows that cases may occur about sixteen years after exposure to the irritant, and many as late as sixty years after first contact and often many years after retirement.

Earlier sections give an interesting account of the history of the subject.

The Problem of Lupus Vulgaris. By ROBERT AITKEN, M.D., F.R.C.P.E. Pp. 69, with 31 illustrations (15 in colour). Edinburgh: E. & S. Livingstone. 1946. Price 15s. net.

This little book embodies the author's practical experience in the care of patients suffering from lupus vulgaris. After discussing the clinical features, almost half the volume is taken up with the treatment of the condition. The chapters on ultra-violet irradiation and tuberculin are especially full and informative. The public health and social implications of the disease are discussed, and a very moving appeal made on behalf of those unfortunate sufferers. This book deserves to be widely read by the medical profession, especially by those engaged in the public health services and by social workers of all kinds. It is beautifully printed and illustrated, the coloured photographs being particularly fine. We would congratulate the author on his succinct, lucid and very readable presentation of the subject.

Essentials of Clinical Allergy. By S. J. TAUB, M.D. Pp. x+198, with 16 plates. Baltimore: Williams & Wilkins Co. London: Baillière, Tindall & Cox. 1946. Price 16s. 6d.

The author has written this book with the idea of clarifying the field of allergy for the general practitioner who cannot devote the time required to study the voluminous and rather controversial literature on allergy. He has presented a practical, clinical approach to the subject and has avoided highly theoretical discussions which have no practical implications.

Dr Taub points out that allergic factors enter into nearly every branch of medicine and the possible allergic nature of many diseases whose etiology is at present unknown may further broaden this specialty.

This little book can be thoroughly recommended.

An Introduction to Essential Hypertension. By R. F. HERNDON, M.D., F.A.C.P. Pp. ix+87, with 4 coloured plates. London: Baillière, Tindall & Cox. 1946. Price $2.50.

With advancing knowledge, the subject of hypertension is forcing its way to the top of the list of medical problems and the literature on the subject is already enormous. The author has aimed to give a simple concise statement of the present concept of the process and to present it in such a way that it should be of the greatest help to the general practitioner. In this he has succeeded admirably, and the book can be confidently recommended to all who are interested in this important subject.

Microanalysis in Medical Biochemistry.   By E. J. KING.   Pp. viii+168.   London:
     J. & A. Churchill Ltd.   1946.   Price 10s. 6d. net.

This small book covers the majority of routine estimations carried out in the
biochemistry laboratory of the modern hospital.   Most of the methods described
have been adapted for the use of small volumes of blood and plasma ; many of the
modifications being the direct result of investigations by Professor King and his
colleagues.

The methods are very well described and the chemical instructions are clear.
In addition to the routine analyses, there are brief chapters on spectroscopic procedure,
tests of function and, of especial importance, on colorimetric and photometric measure-
ments.   This book should be of great value in the laboratory, and it is to be hoped
that the author will expand the range of subjects in future editions.

Physical Chemistry of Cells and Tissues.   By RUDOLF HOBER.   Pp. xiii+676.
     London : J. & A. Churchill Ltd.   1945.   Price 42s.

This volume sets out to elucidate modern physiology in terms of cell function,
treating the subject as a branch of physical chemistry.   The author and his
collaborators assume that the reader possesses not only a considerable knowledge
of mathematics and physics, but also a fairly extensive library on these subjects.
Consequently, the book is not one which will appeal to the average medical reader.

The early sections are mainly mathematical and physical.   In the later sections
of the book the authors consider the applications of thermodynamics to physiological
functions, including respiration, oxidation, the biochemistry and physiology of
muscle, and intestinal and kidney function.   These later chapters, couched in more
physiological language, should be of interest, not only to biochemists and physiologists,
but also to those concerned with research on the clinical side.

Throughout the text the authors are concerned with the functioning of the actual
cell, as distinct from the intact animal.   The pictures so obtained are discrete and the
book does not aim beyond this ; yet one can visualise further advances in medical
science (especially in the field of cancer research) based upon the fundamental facts
which have been so carefully pieced together by the authors.

The book contains a very full bibliography.

Modern Psychiatry.   By WILLIAM S. SADLER, M.D.   Pp. xii+896.   London:
     Henry Kimpton.   1945.   Price 50s. net.

This is a large book which covers a wide field and contains much interesting and
valuable information.   It cannot be read as a whole, but must be regarded more as a
work of reference, dealing particularly with diagnosis and treatment.   It is obvious
that the author has had wide clinical experience, as a result of which he has formulated
his own views in relation to the understanding and treatment of his fellow-men.
His opinions are expressed with considerable dogmatism.   He seems to believe,
however, more in exhortation than in reasoned judgment.

A book such as this has its place and can be helpful to the general practitioner
and to those interested in mental hygiene and personality studies.   It is not a book
which would be suitable for either the undergraduate or the postgraduate specialist.

Men Under Stress.   By R. R. GRINKER and J. P. SPIEGEL.   Pp. xii+484.   London :
     J. & A. Churchill Ltd.   1945.   Price 25s. net.

This most interesting book deals almost exclusively with American Air Force
personnel, and proves that under sufficient stress any individual may fail to adapt
to his difficult circumstances and may exhibit neurotic symptoms.   The book attempts
to understand the psychological mechanism of normal individuals in situations of
stress.   This, therefore, is a valuable contribution because it enables one to judge
one's fellow-men at a much more reasonable and charitable level.   The studies are

important in relation to men who have been engaged in operational work overseas, and also in combat veterans who have returned home for rest and rehabilitation. The case records are first class and constitute a graphic picture of the backgrounds and of the ordeals to which these men were exposed. It is of particular importance that the cases have been followed through, and many who had been examined immediately after their breakdown were again reassessed in the United States.

This is the most comprehensive and most satisfactory war book on war personnel problems which has been published. It can be strongly recommended to all medical men in the Services, and particularly to every psychiatrist.

Handbook of Psychiatry. By LOUIS J. KARNOSH and EDWARD M. ZUCKER. Pp. 302, with illustrations. London : Henry Kimpton. 1945. Price 25s. net.

This book, designed especially for general practitioners, consists of a condensed presentation of psychiatry, inclusive of mental deficiency and the psychoneuroses. It is inevitable that such a book should be dogmatic, but to constitute a safe guide it should also be strictly accurate and practical. Unfortunately it fails to reach those standards.

As an example of the doubtful views expressed, it is stated that " castration is found beneficial to the sexually aberrated person and to the public at large."

The book cannot be recommended.

A.B.C. of Medical Treatment. By E. NOBLE CHAMBERLAIN, M.D., M.SC., F.R.C.P. Pp. viii+206. London : Oxford University Press. 1946. Price 10s. 6d. net.

A brief account of the treatment of the more common medical ailments is given under the names of diseases and symptoms arranged alphabetically. The notes are exceedingly short, but seem to contain the essential features. The author is frankly critical of many accepted procedures and states his opinions clearly. Some sixty pages are devoted to detailed diets, and these should prove very helpful.

The book is primarily intended for the general practitioner who wishes a handy reference, and it should adequately meet this need.

Anatomy and Physiology for Nurses. By J. L. HAMILTON-PATERSON, M.D. Pp. vii+174, with 102 illustrations. London : H. K. Lewis & Co. Ltd. 1946. Price 9s. net.

In the small scope of 174 pages the author has covered those elements of two large sciences which are necessary for those who are appearing for the preliminary State examination in Nursing. The first chapter is of a very general character, then follows a short description of the physiology of the body and a general account of structure. Next there is a description of histology and the physiological mechanisms which depend on microscopic structures, and the later chapters give a more detailed account of the regional anatomy of various parts of the body. The scheme is excellently carried out, the explanations are clearly given and the text is well illustrated by simple line diagrams. The book will serve a useful purpose.

Artificial Respiration Explained. By F. C. EVE, M.D., F.R.C.P. Pp. iv+76, with 32 illustrations. Edinburgh : E. & S. Livingstone. 1946. Price 3s. net.

The author points out that the subject of artificial respiration usually receives scant attention in odd corners of books on First Aid. He feels so much advance has recently been made in the subject that it now justifies more attention. Underlying principles and objects are described in simple language and the various methods in current use are thoroughly examined. The book should be of the greatest service to those who wish to prepare themselves to render first aid.

NEW EDITIONS

Medical Jurisprudence and Toxicology. By JOHN GLAISTER, J.P., D.SC., M.D., F.R.S.(Edin.). Eighth Edition. Pp. xii+691, with 222 illustrations, 89 in colour. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 30s. net.

This edition has been thoroughly revised and brought up-to-date and many new illustrations have been included. Much new material has been added in relation to the English and Scottish courts and the relevant legislation throughout has been revised. The toxicological section gives an account of many new substances and the subject of alcoholism is discussed at length. The high standard set by the previous editions has been fully maintained.

The volume will make a substantial contribution to forensic medicine and will prove of great value to both lawyers and medical practitioners.

Chest Examination. By RICHARD R. TRAIL, M.C., M.A., M.D., F.R.C.P. Second Edition. Pp. x+122, with 94 illustrations. London: J. & A. Churchill Ltd. 1945. Price 12s. 6d. net.

This little book has been written mainly to correlate the anatomy and physiology of the lungs with the physical findings—clinical and pathological. The present edition has been slightly enlarged, particularly by the addition of illustrative X-rays, set in the text so that they are easy for reference. The order of contents has been changed and notes added on such points as the interpretation of breath sounds and the " natural abnormalities " of the bony thorax.

Symptoms of Visceral Disease. By FRANCIS MARION POTTINGER, A.M., M.D., LL.D., F.A.C.P. Sixth Edition. Pp. 442, with 97 illustrations and 10 coloured plates. London: Henry Kimpton. 1944. Price 25s. net.

This book attempts to bring an important phase of physiology to the physician. Some symptoms are easy to interpret, others, mainly of a reflex nature, are more difficult. The author discusses man as a segmental organism, and assigns reflex spasms, referred pain and degenerations to the various neurons which mediate impulses from inflamed or irritable viscera. The clinician, knowing these segmental relationships, can hence reason from the affected organism to the zone of the reflex or from the zone of the reflex back to the organ.

Clinical Biochemistry. By A. CANTAROW and M. TRUMPER. Third Edition. Pp. 647, with 29 illustrations. London and Philadelphia: W. B. Saunders Company. 1945. Price 32s. 6d. net.

This book will prove to be extraordinarily useful to those who are interested in the applications of Biochemistry to Clinical Medicine. There is a sufficiency of elementary biochemistry in the various chapters to make the book acceptable to those who have not specialised in chemistry, and who yet would be prepared to learn a little of the subject for the sake of advancing their knowledge of scientific medicine.

The text is clearly written, the arguments are easily followed, the whole material is brought more up-to-date than one has any right to expect at the present time, and it covers a very wide range of scientific and medical research. It is a book which one would have great confidence in recommending to clinicians who are interested in the scientific side of medicine.

The indexing is up to the highest possible standards, and there are over a thousand useful references. It is significant to note that only about 5 per cent. of these refer to British publications.

Clinical Pathology. By P. N. PANTON, M.A., M.B., B.CHIR., and J. R. MARRACK, M.A., M.D., with the assistance of H. B. MAY, M.A., M.D., M.R.C.P. Fifth Edition. Pp. ix+450, with 59 illustrations. London: J. & A. Churchill. 1945. Price 21s. net.

In this book full details of the chemical, bacteriological and histological procedures demanded of a clinical laboratory are given. Many of the tests are those also used by clinicians, for whom a list of the samples required by the laboratory for chemical analysis is now included. The methods described are not always those in most common use, but there can be few investigations, even those most recently suggested, which are not covered by the tests given. Additions to the present edition include a section on antibacterial chemotherapeutic substances and a sub-section on the Rh agglutinogens.

The findings in health and disease are clearly stated and though the discussion of the significance of abnormal findings is condensed, it should be of use to the laboratory worker for whom it is primarily intended, if not to the clinician.

Diseases of the Nervous System. By F. M. R. WALSHE, M.D., F.R.C.P., D.SC. Fourth Edition. Pp. xvi+360, with 51 illustrations. Edinburgh: E. & S. Livingstone Ltd. 1945. Price 15s. net.

The fourth edition of Walshe's *Diseases of the Nervous System* is a clear and eminently readable account of the commoner nervous diseases. Factors in neurological diagnosis are discussed in the opening chapters ; the book ends with a short account of the psychoneuroses and includes a very practicable and simple scheme of examination of the nervous system.

Progress in knowledge since the publication of the third edition has called for revision ; several chapters have been throughly recast and new matter added on the nature of ætiology and on the concept of psychomatic illness.

Dr Walshe has his foibles ; his reluctance to honour great clinicians of the past in the matter of nomenclature leads to the appearance of a few unfamiliar terms. Korsakow's syndrome, for instance, is referred to as the polyneuritic psychosis. As a whole, however, the book affords the best approach to neurological illness for students and general practitioners that I have read.

A Textbook of Ophthalmology. By SANDFORD R. GIFFORD, M.A., M.D., F.A.C.S. Third Edition. Pp. 470, with 260 illustrations including 43 in colour. London : W. B. Saunders and Co. Ltd. Price 20s. net.

This short textbook by the late Dr Sandford Gifford can be recommended to students and general practitioners as both reliable and readable.

Many ophthalmologists, however, would disagree with the emphasis laid upon certain lines of treatment. Few, for example, would agree that intensive therapy with vitamin B1 is of proven value in the treatment of retrobulbar neuritis due to multiple sclerosis, or that heparin has been shown to have appreciable effect in lessening the damage resulting from thrombosis of the central retinal vein. The value of riboflavin in the treatment of acne rosacea would also appear to have been over-stressed.

Introduction to Medical Science. By WILLIAM BOYD, M.D., M.R.C.P.E. Third Edition. Pp. 366, with 126 illustrations. London : Henry Kimpton. 1946. Price 18s.

The title of the book is perhaps rather misleading. It is written for the nurse beginning her medical career and is planned to give a general introduction to the study of disease, its causes, and the changes which accompany it.

Professor Boyd is the author of several successful text-books. His clear style and apt descriptions contribute greatly to the popularity of his works.

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ABDERHALDEN, EMIL, Professor an der Universitat Zurich. Lehrbuch der Physiologischen Chemie . . (*Benno Schwabe & Co., Verlag, Basel*) —

BAILLIF, RALPH N., PH.D., and KIMMEL, DONALD L., PH.D. Structure and Function of the Human Body . . (*J. B. Lippincott Co., London*) 18s. net.

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HERNDON, RICHARD F., M.D., F.A.C.P. An Introduction to Essential Hypertension . . (*Charles C. Thomas, Publishers, Springfield, Illinois*) —

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THE PROGRESS OF DERMATOLOGY

INAUGURAL ADDRESS

By Professor G. H. PERCIVAL

ALTHOUGH the chair of Dermatology is the first of its kind to be established in Great Britain, the subject with which it is concerned has occupied the attention of the medical profession from the earliest times. Not only have British physicians played a prominent part in its development but, as in other branches of medicine, graduates of this University have been numbered amongst its most distinguished exponents.

To me has fallen the great honour of being the first occupant of the chair, and it seems fitting that in my inaugural address I should trace the past development of my subject, give an account of its present state, and discuss its future.

HISTORICAL

The roots of dermatology are as deep as those of medicine itself. The Ebers Papyrus describes skin diseases and their remedies, and Herodotus tells of an ancient dermatologist who was called in consultation from Egypt to Greece. In the Old Testament the Pentateuch records a plague of boils and blains ; the Levitical dispensation gives guidance to the priesthood in the general management of skin disease ; and Job's eruption, which greatly aggravated his general distress, is described in detail.

In the Hippocratic collection, and later in the works of Aristotle, Galen, and Celsus are to be found many dermatological names with which we are familiar to-day. One observation calls for more than passing notice, in view of subsequent events, and on account of its general interest : this is the mention by Aristotle of the existence of the parasite which we now know as the acarus scabei. He drew attention to the fact that it lives *in* the skin, but he did not regard it as the cause of scabies, and two thousand years and more were to elapse before its etiological significance was recognised by the medical profession.

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At a later date the Arabians gave accurate descriptions of variola and rubeola, leprosy and madura foot ; they enlarged on previous

conceptions of pemphigus, eczema and rosacea, and *they also* noted the acarus as being incidental to the skin.

As in other fields of medicine, little was added to our knowledge of skin diseases throughout the Middle Ages and early Renaissance, when physicians occupied themselves by debating the writings of the ancients and speculating on humoral causes to the neglect of *clinical* study. At this time, however, there were two occurrences of outstanding dermatological interest. The first was the spread of leprosy throughout the European continent, coinciding with the wanderings of the crusaders and the general state of poverty resulting from constant warfare. The second was the introduction of syphilis to the old world. The contagiousness of leprosy had been early recognised, and steps were soon taken to limit its spread by the institution of leper houses. At one period there were estimated to be some 19,000 throughout Christendom. It must not be supposed, however, with the confused terminology which then existed, that the diagnosis of leprosy was accurate, and probably many sufferers from a variety of benign, chronic, and ulcerative skin conditions were put into Lazar houses and true lepers were much in the minority.

Syphilis was brought into Western Europe at the end of the fifteenth century, the disease spread rapidly throughout the entire civilised world, and in the words of a contemporary French writer "spared not cross nor crown." Its skin lesions were of course most prominent, and its constitutional accompaniments of a severity to cause great suffering and early death. The credit for presenting the first clear picture of the symptoms and course of this new disease is usually given to Fracastorius, a Veronese physician, who made it the subject of a Latin poem which he published in 1530. But I should like to point out that William Dunbar should at least share the poetic and clinical laurels with Fracastorius, and even take pride of place; for in 1500 he wrote and published a poem on syphilis, in which he described many symptoms of the disease, and which he dedicated to the queen of King James the Fourth of Scotland. In Scotland, syphilis was originally designated "gore" or "grangore," and in 1497 an edict was drawn up by the King's Privy Council in Edinburgh entitled "Ane Grangore Act," ordering that precautions be taken to prevent the spread of its contagion. That the authorities were alive to the necessity for preventive measures is evidenced by two Ordinances issued as far apart as Paris and Aberdeen—in Paris on 6th March 1497, and by the Aberdeen Town Council exactly forty-five days later (21st April).

During the sixteenth and seventeenth centuries, just as syphilis was becoming endemic throughout Europe, and its symptoms, though still severe, were lessening in intensity, leprosy showed a rapid decline, and Daniel Turner, writing in London in 1714, claimed no personal knowledge of it whatsoever.

There was no orderly classification of skin diseases. The current nomenclature, including the terms leprous and scorbutic, was applied

indiscriminately to any and every cutaneous eruption, and had no true diagnostic significance.

In this state of virtual chaos the first book devoted entirely to diseases of the skin was published by Girolamo Mercurialis at Venice in 1572. It was not until 1714 that the second appeared—the work of Daniel Turner, of the College of Physicians of London. This book achieved great popularity, reached a fifth edition, and was translated into French in 1742, being the first dermatological treatise in that language. Turner described a variety of skin diseases, without any attempt at classification beyond arranging them according to the region of the body which in his experience they commonly affected.

It is interesting to reflect that the visual perception of colour and form is, with few exceptions, and without the aid of even the simplest apparatus, the sole faculty required to differentiate the various skin diseases. One might even go further and say that a keen appreciation of colour is the less important of the two. Both the history of dermatology and present-day experience in teaching it to students who have already been to some extent trained in clinical observation seem to show that the faculty of keen visual observation is relatively dormant ; certainly in comparison with the faculty of recording aural and tactile impressions and of understanding the written or spoken word.

In the last decade of the eighteenth century, however, there was one physician, by name Robert Willan, in whom this faculty was developed in the highest degree. He was indeed " Eyes to the Blind," and he has been acclaimed with justice as the father of modern dermatology. Robert Willan graduated at Edinburgh University in 1777, his years of active medical practice were spent in London, and he died in Madeira at the age of fifty-three. In 1790 he had evolved his plan for the arrangement and description of cutaneous diseases, and for this great work he was awarded the Fothergillian Gold Medal by the Medical Society of London.

He classified skin diseases according to the predominant primary lesions, a method which is essentially artificial, which is based on external appearances only, and which takes no account of the intimate nature, course, or cause of the disorder. Like most other classifications of natural phenomena it is open to criticism, but of all those suggested in dermatology that of Willan has best stood the test of time. Since Willan's day the nomenclature of skin disease has been further enriched by many imposing titles which have been perhaps from time to time the subject of kindly criticism on account of their apparent extravagance. But copious and definite nomenclature has manifest advantages ; it demands an accurate investigation and a habitual analytic turn of mind, and where there is little discrimination in language, little precision in observation can be expected.

Willan had for his assistant and colleague Thomas Bateman, who was also a graduate of Edinburgh University, and who continued the work of his teacher and was instrumental at that time in spreading

Willan's views more widely than might otherwise have been the case. Bateman's main work was translated into several languages, and not only did it receive a most cordial reception by the medical profession but it met with the approbation of no less a personage than the Emperor of Russia.

During this period, France, even while recovering from the agonies of a profound political upheaval and engaged in a prolonged and disastrous war, was quick to absorb and apply these new principles, and during the succeeding decades the scene of dermatological activity and progress, initiated in Britain, shifted to the St Louis Hospital in Paris.

Jean Louis Alibert, afterwards Baron Alibert, was then working in the hospital, and had as his contemporaries in other branches of science and medicine such men as Lavoisier, Lugol (of iodine fame), and Dupuytren. Alibert devoted himself exclusively to hospital practice during the period of the Napoleonic wars, and dermatology was his main interest. In 1815, in contrast to the modern conception of ideal conditions of medical service, he forsook his full-time hospital appointment for a remunerative practice in the circle of the restored monarchy, thus emulating Vesalius, who evinced a similar change of heart some two hundred years before him. Alibert, however, saw the error of his ways, and in 1829 he returned to the scene of his former triumph, where he spent the remainder of his days as a stimulating teacher and a no less vigorous adversary of Willan's views, which, during the Baron's absence, had been introduced to the St Louis and generally accepted by its staff in preference to his own.

In the middle of the nineteenth century a progressive school of dermatology was established in Vienna by Hebra, with his able successor, Kaposi. They made full use of the discoveries of their predecessors, but contributed little new themselves. In the latter part of the century Paul Unna of Hamburg was perhaps the most dominant personality in the world of dermatology. He was quick to adapt to the study of skin diseases the newly discovered science of bacteriology and the improved technique of histo-pathology, but either because of his dogmatism or of misinterpretation of the real meaning of certain of his hypotheses and statements his teaching has subsequently been the cause of no little misunderstanding in some fields of dermatology.

At this time no attempt had yet been made in London to provide any systematic teaching in dermatology, and in the various hospitals and dispensaries patients suffering from skin disease were relegated to the charge of some junior member of the staff whose real ambition lay in other directions. Nelligan, Erasmus Wilson, and Tilbury Fox had carried on the tradition of Willan and Bateman, but dermatology was receiving no recognition as a special subject. In 1882 a group of physicians who were interested in diseases of the skin formed the Dermatological Society of London; in 1888 the British Journal of Dermatology was founded, and the London School of Dermatology

gradually took shape. It was soon sponsored by such renowned figures as Malcolm Morris, Radcliffe Crocker, Jonathan Hutchison, and many others.

PROGRESS IN SCOTLAND

Having outlined the slow evolution of world dermatology to a stage where some semblance of maturity and definition has been achieved, it is only consistent with the present occasion that we should review the progress of dermatology in Scotland, and particularly its development here in Edinburgh.

Our early records show that leprosy and syphilis flourished in Scotland as elsewhere, and the prevalence of skin diseases in the Highlands in the early eighteenth century is mentioned by Macauley, who quotes from Burt's letters and Clelland's poetry to show that many of the inhabitants were covered with cutaneous eruptions and smeared with tar, like sheep.

A lively contemporary interest was naturally taken by the medical profession of Edinburgh in the teaching of Willan and Bateman, and critical reviews of both Willan's and Alibert's classifications appeared in the Edinburgh Medical and Surgical Journals of 1806 and 1820. These show that the reviewers were not only thoroughly acquainted with the prevailing views on dermatology but were highly appreciative of Willan's work. In 1821, Thomson, then professor of pathology, observed and described a series of cases of molluscum contagiosum, a condition which was not previously well known—Willan was not familiar with it—and one which has remained since Thomson's time essentially an Edinburgh disease. In 1824 an attempt was made by Dr Edward Duffin to establish a Skin Dispensary in Edinburgh, when on his own initiative he opened a clinic in the Lawnmarket. He not only examined three hundred new patients there in the first two months but in his own residence provided bathing facilities, and during the same period five hundred baths were administered to the suffering poor. Duffin tried to raise funds to further these projects, but unfortunately his appeal, in which he used exactly those arguments which have been used so often on subsequent occasions for similar purposes, met with no response, and his clinic had to be discontinued. Thus the first of several efforts to establish dermatology in Edinburgh failed.

Some time later, in 1831, John Paget graduated in Edinburgh University, proceeded immediately to Paris and studied dermatology under Alibert. In 1832, against considerable international competition, he succeeded in gaining a prize which had been offered by Alibert for a dissertation on the relative merits of the artificial and natural classification of skin diseases. This early promise did not mature, however, for on leaving Paris he married a Polish baroness, and thereafter interested himself in the management of his wife's estates, in which occupation he seemed to excel, for he became noted as an agriculturist, introduced a new breed of cattle, and devoted particular

attention to the culture of the vine. In spite of his obvious good fortune and useful life it must be deplored that he did not choose to return to his native city, there to further the subject in which he had shown such initial prowess.

Sir Norman Walker often recounted how he had inquired of two Edinburgh students of the forties of last century, Sir Henry Littlejohn and Dr John Smith, what were their recollections of the teaching of dermatology in the University in those days. He was told that it was non-existent, and that no case of skin disease was admitted to the clinical wards or received treatment of any description. Paris was then the only centre where dermatological instruction was available. This grave omission from the medical curriculum was rectified by Dr Hughes Bennett, to whom the Edinburgh Medical School also owes much for his introduction of a new and methodical system of clinical teaching based on personal observation, and the education of the senses. Here are some of Bennett's remarks on diseases of the tegumentary system, quoted from his *Principles and Practice of Medicine*:

" Ignorance here, although it seldom occasions danger to human life, produces great inconveniences, exasperates the progress of other maladies, renders life miserable, and frequently destroys those social relations and ties which constitute happiness."

Bennett shared the skin wards with Laycock, the professor of Medicine, each being in sole charge for three-monthly periods, and *it is said that each was capable of the most open and robust criticism* of the other's views and methods, a state of overt rivalry which must surely have been in the best traditions of the subject and must have provided added interest for the student.

Bennett died in 1875, and when the present Infirmary was opened in 1879 no wards were set aside for the treatment of skin diseases. The foundations which he had laid for the establishment of dermatology in Edinburgh were thus abandoned, and apart from a slight interest in skin diseases shown by Sir Douglas MacLagan, who from time to time admitted cases to his wards, the subject passed into a period of temporary oblivion. In 1880 Sir Norman Walker began the study of medicine, and his chief recollection of the instruction he then obtained in the subject to which he was later to devote himself with such distinction was that Joseph Bell taught him to distinguish between rodent ulcer and lupus vulgaris, a differentiation which some at least of Bell's colleagues regarded as being hardly worth while.

Allan Jamieson graduated in Edinburgh in 1865, and his interest in skin diseases had been aroused by the teaching of Hughes Bennett. After a short spell of general practice in Edinburgh, Jamieson, on the advice of Sir Douglas MacLagan and Argyll Robertson, decided to specialise in diseases of the skin, and after a period of study under Hebra he returned to Edinburgh to carry out this project. He met with considerable opposition from the older physicians, and it was not until 1884 that he was appointed to the Staff of the Royal Infirmary as Extraordinary Physician for Diseases of the Skin.

Jamieson had first one—later extended to two—out-patient days in the week, and he established his reputation as a dermatologist and a teacher by the publication in 1888 of his *Manual of Diseases of the Skin* and by his almost legendary Saturday morning clinics in the West Medical Theatre.   His success as a teacher clearly indicated that a systematic course of dermatology should be included in the medical curriculum, and after a prolonged process of wearing down vested interests this last ditch was carried, and the University appointed Allan Jamieson Lecturer in Dermatology.

At this time events relating to dermatology were moving on parallel lines in Glasgow and were being sponsored by McCall Anderson. In 1861 he organised and opened the Glasgow Hospital for Diseases of the Skin, and in 1883 a special department for Diseases of the Skin was established in the Glasgow Royal Infirmary.

Returning again to affairs in Edinburgh, Ward I was allocated jointly as an Ear and Throat and Skin department in 1891, and Jamieson shared its twelve beds with Peter Macbride, but the popularity of Jamieson's lectures was for a time the unwitting obstacle to the further expansion of the Skin Department, for the following reason.   In the minutes of the Royal Infirmary for May 1899 it is recorded that a request by him for additional beds was refused by the Managers on account of the unanimous disapproval voiced by the Medical Staff, who were of the opinion that Jamieson's classes had a deleterious effect on the attendance at their medical clinics. The measure of protection afforded by the Managers to the Senior Physicians was, however, of short duration, and in 1903 when the new Ear and Throat Department was opened, Jamieson fell heir to six additional beds.   The opening of the new Eye Department in 1905 vacated space in Ward II, which had long been associated with the name of Argyll Robertson, and this in turn was given over to the Skin Department, which from that time until 1936 was located in Wards I and II.   Jamieson retired from the Infirmary in 1906, and to his ability and statesmanlike qualities lies the credit of at last establishing dermatology on a firm footing in this school, thus fulfilling Bennett's earlier ambitions.   In a recent reference to Jamieson and McCall Anderson, Sir Ernest Graham Little has aptly described them as the two pillars which support the imposing edifice of Scottish Dermatology. Sir Norman Walker succeeded Jamieson as the holder of the Lectureship, and it requires no words of mine to recall the worthy manner in which he filled this office, or to remind you of his untiring efforts for the advancement of medicine, for his memory is still green amongst us.   He was a clinician of outstanding ability, and, like Allan Jamieson, a gifted teacher and writer.   His book, *An Introduction to Dermatology*, first published in 1899, reached its tenth edition during his lifetime. Through his initiative the treatment of ringworm of the scalp and lupus vulgaris was put on an organised basis in Edinburgh ; he was a pioneer in X-ray therapy, and bore the evidence of it on his hands ; and the collection of models of skin disease at present owned by the

University, and which is second to none, was begun under his auspices. He would surely have rejoiced had he known that in the fullness of time his own subject was to receive such ample and generous recognition as it does to-day.

In 1912 Dr Frederick Gardiner was appointed joint lecturer in Skin Diseases with Sir Norman Walker, with whom—and later with Dr Cranston Low—he shared the Skin Wards. Finally, in the month of June 1936, a new Skin Department was opened in the Infirmary, the most complete of its kind in Great Britain.

HOSPITAL ORGANISATION

This now brings me to the point where the romance and history of the subject end, and where we must consider and appraise what we find here in Edinburgh, and suggest improvements. It is not of course possible even to guess at the real incidence of skin disease in the community, but it is safe to say that in recent years at least 20,000 patients suffering from skin disease are seen each year in this area by dermatologists alone. In 1940, centres for the treatment of cutaneous parasitic infestations and their septic complications were established in Edinburgh, and have dealt with some 25,000 cases annually. Daily out-patient dressings at the rate of approximately 12,000 per annum are given in a small department for this purpose attached to the Skin Department of the Royal Infirmary, and at a special centre for the treatment of school children the figure is in the region of 7000. In the various skin wards of the Infirmary and the Municipal Hospitals the annual admission rate is approximately 600. These figures are sufficient to show that there is no lack of material for clinical observation and investigation, and they show a significant increase on those of the newly extended Skin Department of the Edinburgh Royal Infirmary in 1908, when the number of cases seen and treated was only 1600.

This increase in the incidence of skin disease is certainly more apparent than real, and probably indicates a greater attention to health on the part of the public, and an appreciation of the facilities available to them. The general incidence of skin disease depends partly on housing conditions, partly on the extent to which the public avail themselves of the facilities provided in new housing schemes, and by the town authorities, and partly on school medical inspection. If these services are adequate and properly used the incidence of parasitic skin diseases and their septic complications will be kept down. The general nutrition of the community, and the existence of circumstances predisposing to anxiety and nervous strain have a direct bearing on the occurrence of other groups of skin disease, and conditions in industry greatly influence the incidence of dermatitis.

The first mention of industrial dermatitis was made by Ramazzini in 1705 in his *Treatise on the Diseases of Tradesmen*, in which he quotes Hippocrates as saying " that there are very many arts and

callings which are very useful and pleasant to those who stand in need of their assistance, but occasion a great deal of trouble and labour to those who practise them." Conditions of working are much improved since the days of Ramazzini, and general intoxications as a constant risk have been almost entirely eliminated from industry. Although it is a compensatable disease there is no compulsory notification of industrial dermatitis, but of cases notified voluntarily there were in 1937-38, 2500; in 1942, 9500; and in 1943, 8802. These numbers are from five to nineteen times greater than those for the fourteen *notifiable* industrial diseases for the corresponding years, and in one industry the figures obtained from a single district seem to indicate that the incidence of dermatitis has increased seventy-fold during the past five years. Much has been done to try to reduce dermatitis in industry by giving the workers protective garments, protective creams for application to the skin when exposed to the action of dusts and liquids, and by the provision of adequate washing accommodation. In spite of this a considerable number of cases are attributable to carelessness on the part of the worker, needless exposure of the skin to known irritants, and to neglecting to use the protective measures provided. The rehabilitation of cases of industrial dermatitis is difficult, for it is seldom possible for a manual worker to obtain dry, clean, work, and an immediate return to any other type of employment is fraught with the risk of recurrence. The housewife is perhaps the most unfortunate sufferer from the disease—for her there is no compensation, no possible change of employment, and if the incidence of dermatitis in the great national industry of housekeeping were known, the figure would without doubt be staggering.

If such is the bearing of the social environment on dermatology, what is the outlook for the individual sufferer from skin disease? In the vast majority of cases the diagnosis of skin disease is rapid and accurate, but their cure is another matter, and treatment is often a weary process. Disease of the skin differs from that of most other organs in that it is *visible* to the patient as well as felt by him, and no cure is complete from his point of view until he no longer experiences its sensations and can no longer see his eruption. In this latter respect the internist, with his apparatus and laboratory reports, and the situation of the organs whose diseased states he treats, is often in a much more enviable position *vis-à-vis* his patient, and perhaps his own peace of mind, than his dermatological colleague. Nevertheless it is possible with care and perseverance, and given adequate facilities, to influence favourably or to cure almost all skin diseases, many of which would, if left to themselves, be of a more or less continuous and permanent nature. Unfortunately this ideal is not invariably achieved in general practice and for the following reasons. Because skin disease is seldom dangerous to life, and seldom causes complete incapacity, the patient may be unwilling to undergo a form of treatment which keeps him from his normal pursuits, and in many cases treatment may have to be modified to suit the patient and not the disease. Further-

more, under present conditions we so often have to leave the patient to carry out a complicated and time-consuming dressing without adequate help, facilities, or supervision. The average patient may be entrusted with the oral administration of a potent drug, and the most satisfactory results are obtained, but when he is faced with the task of personally treating an eruption of even moderate extent it is unlikely that the instructions will be followed with equal precision. Such a condition should be treated for him by a nurse with special knowledge of the appropriate technique, but it is at present seldom possible to obtain this necessary help. There is a general shortage of nurses, and a proportionately greater shortage of nurses who have any dermatological experience. A long and arduous training is necessary before a nurse becomes expert in the treatment of skin diseases, and many more nurses possessing such specialised knowledge are required to meet present-day needs. The treatment of a skin disease demands patience and attention to what appear at first to be trivial details, but what training could be better in a nursing course, for the nurse can see the effects of inattention to detail, and she can have the satisfaction of watching the disease fade before her eyes as a result of well-directed effort.

There exists in Edinburgh the nucleus of a scheme for the nursing of out-patients suffering from skin disease, but it is not sufficiently organised, nor is it large enough to deal with the needs of the City and its immediate surroundings. It comprises too many unco-ordinated centres, some of them makeshift war-time arrangements, some of them ill-housed, and in at least one the conditions under which the staff carry out their duties and in which the patients wait and are treated, are quite unsatisfactory. The convenience to the community intended by the regionalisation of certain centres has been defeated to some extent by the fact that many sufferers from skin disease hesitate to seek help at treatment centres in their own district because they feel that by doing so the nature of their ailment may become known to their neighbours. A single well-equipped, completely staffed, and centrally placed establishment would bring about an economy in administration, would save much loss of time in school attendance and in industry, and would alleviate considerable suffering and inconvenience. We need more bed accommodation, and, as far as ordinary skin diseases are concerned, it should, if possible, be housed under one roof. Separate accommodation should also be provided for the treatment of the prolonged case, for certain diseases may require from two to three years' constant treatment for their cure, and the way of the sufferer from lupus should certainly be smoothed by the establishment of a properly equipped treatment centre, with beds attached. In these three ways—by the provision of a larger number of specially trained nurses, the establishment of an adequate out-patient treatment centre, and by increasing and centralising the existing bed accommodation—the immediate social burden imposed by skin diseases would without doubt be considerably lightened.

TEACHING

Such is the position from the point of view of organisation but, without the practitioner and the specialist, what has been done and what is envisaged could not be, and this brings us to a consideration of the teaching of dermatology, which is obviously a prime concern of the chair.

I do not wish to elaborate a plan wherewith to revolutionise the organisation and teaching of a subject which has reached its present state by a slow process of evolution, but some enterprise from which new plans may evolve is essential to the vitality of the subject. It seems that the student has difficulty in acquiring an understanding of skin disease. It may be that the nomenclature sounds unduly strange to his ears, or that the points of clinical differentiation are finer than those which he has already encountered in his course. He may be confused by the fact that a single eruption can present a variety of appearances according to the region of the body which it affects and as a result of external influences from which the internal organs are protected. Perhaps it is because the entire disease is too obviously spread out before him, demanding an immediate and absolute interpretation. I have already referred to the rôle of visual observation in dermatology, and to the seeming poor development of this faculty with regard to static objects, but if the student has not eyes to see and a visual memory to store the picture no words however eloquent can aid him. To make good this shortcoming would seem to be an admirable exercise for the student, and to master it would increase his facility in other subjects in the medical curriculum. No other clinical subject can develop this faculty to the same extent, and it might therefore be advantageous to introduce him to dermatology at an earlier stage in the curriculum. He would have an opportunity of *visually* observing diseases run their course and would correlate cellular pathology and derangement of function with visible clinical findings, and not with sounds and shadows. The histo-pathology of skin disease is more accurately known and more easily accessible than that of any other group of organs; in no other organ can the known facts of the biological conception of allergy be so clearly and easily demonstrated, and the capillaries of the human skin and their reactions provide a striking object lesson in physiology.

With the aid of colour photography, the cinematograph, and in particular, the talking film, the teaching of dermatology to large groups of students can be improved beyond measure, and the adoption of these methods to under-graduate and post-graduate teaching only awaits the availability of the necessary apparatus.

RESEARCH
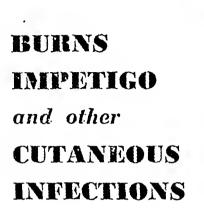
Turning now to consider the scientific aspect, it becomes apparent that dermatology has been the subject of continuous and persevering

research. The outcome of research must of necessity be determined by a mixture of minute observation and inevitable chance, and in the past fortune has, on occasion, favoured the diligence of dermatologists. Dermatological research has played no small part in the advances which have been achieved in medicine since the eighteenth century—a part which is so woven into the accepted fabric of medical thought that in these days it may not be generally recognised, and it is therefore well worthy of mention.

The pioneer work of Robert Willan produced a classification of skin disease, and, by establishing precision where there had previously been utter confusion, he removed the first obstacle in the path of the study of causation. The earliest advance in the etiology of skin diseases was the discovery that the acarus was the cause of scabies. The existence of the acarus had been known for at least 2000 years. In 1687 an Italian naval doctor named Bonomo gave an accurate description of the mite and correctly attributed scabies to its activities, but his observations were overlooked, and in the early nineteenth century scabies was still regarded by the medical profession as an eruption of internal origin due to the melancholy humour of Galen, the corrosive acid of Sylvius, or the ferment of Van Helmont. It is well to note that it was the medical profession which was thus deluded, for the laity had associated the parasite with the disease for centuries. Alibert was a strong supporter of the theory, for to the medical profession it was no more than a theory that the acarus might be the cause of scabies, and for twenty years this idea provoked a heated controversy among the leaders of Parisian medicine. A prize was offered for the demonstration of the acarus in cases of scabies, and several false claims to its discovery were made. Finally, in 1834, a Corsican physician successfully demonstrated the parasite in a series of cases of scabies to a formal gathering of savants, including Duchesne, Raspail, and Lugol.

The next important discovery was the identification of the ringworm fungi by French observers. In Edinburgh Hughes Bennett immediately verified their findings and was one of the first, if not *the* first, to carry out a successful experimental inoculation of favus. Up to this time all conditions of the scalp had been regarded as varieties of one disease of humoral origin which was indiscriminately referred to as Favus, Tinea, or Porrigo.

Considered in the light of contemporary nineteenth century medicine, these were epoch-making discoveries, and they had a most profound influence on the trend of medical thought. The validity of the time-honoured humoral theories was discredited by the recognition of two parasites, the science of human bacteriology was born, and dermatology was for the time being in the forefront of medical progress.

In more recent times noteworthy additions to the knowledge of virus bodies have been made by the study of Herpes Simplex, and particularly through the work carried out in this University on

Molluscum Contagiosum. The discovery of cutaneous vaccination by Jenner preceded by almost one hundred years the commencement of the study of immunity by experiments on the skin with tuberculin. Later, the conception of anaphylaxis and allergy was evolved, and in its advancement the skin has provided a mass of important detail, particularly in connection with the mycotic diseases and eczema. In fact, in the human, the skin is the only organ in which allergic phenomena can be accurately studied, and it has been used as a test tissue to indicate the state of reactivity of inaccessible structures. A multitude of facts have emerged from these investigations, their interpretation has lead to much ingenious speculation, and from them it has been possible to draw a few pertinent conclusions. Without the skin the subject of immunology in its widest sense would be much the poorer.

Modern radio-therapy started its career from the chance observation that X-rays caused a fall of hair, and for many years their use was limited to the production of this biological effect. The unfortunate cutaneous carcinogenic action of X-rays and radium was noted in due course when some of the early experimenters had fallen victims to it, but the first record of a carcinogenic action had been made by Pott in 1775, again in the study of cutaneous cancer. These two observations have provided most valuable information with regard to the causation of malignant disease.

Much has been learned about tissue metabolism by observing the effects of ultra-violet light on the skin in the production of vitamin D, from the experiments of my friend, the late Professor Bruno Bloch, on pigment formation, and from those of Sir Thomas Lewis on tissue metabolities and their action on nerves and blood vessels. Chemotherapy was first employed in the treatment of cutaneous disorders, and the scope and limitations of vaccine therapy have been investigated most profitably in diseases of the skin.

From all this it is evident that the study of the skin has proved in the past a fertile source of new knowledge, and it should be so maintained by the further pursuit of problems which have already been approached, and by exploring new fields.

I can think of no example more worthy of emulation by physician and research worker alike than that set forth by Job—the first recorded sufferer from skin disease—and so simply stated in those words of his which say, " I was a father to the poor, and the cause I knew not I searched out."

The forethought and generosity of Sir Robert Grant have created facilities for research and teaching in dermatology such as never before existed in Edinburgh, the outlook for the subject has never seemed brighter, and it is to be hoped that by constant endeavour the new department will make full use of this great opportunity.

ANTICOAGULANT THERAPY IN THROMBOSIS [*]

By J. ERIK JORPES, M.D., Stockholm

NEXT year, a hundred years will have passed since Virchow coined the term thrombo-embolism and taught us that pulmonary embolism is nothing but the final stage of thrombosis in a leg. The immense literature dealing with the subject which has appeared since then mentions little about successful therapeutic measures. In fact, Morawitz in 1934 confessed that the medical profession was at that time as helpless in the face of acute thrombosis as it had been fifty years earlier. Now the situation has changed : we have in our hands effective agents, heparin and dicumarol, for the prevention of intra-vascular coagulation during life, and by means of them thrombosis and pulmonary embolism can be combated.

HEPARIN

It is now almost thirty years since Howell and McLean [1, 2] discovered heparin, and its chemical structure has been known for ten years.[3] Much has been written about its chemistry and physiology.[4, 5, 6] On the present occasion I will call attention to only two details : its physico-chemical properties and its formation by the mast cells of Ehrlich.

Heparin is a mucoitine polysulphuric acid, and the strongest preparations of heparin contain 45 per cent. of sulphuric acid.[7, 8] It consequently has an exceedingly strong negative electric charge. No other high molecular compound in the animal body has such a strong electric charge. Evidently, heparin exerts its action through this charge. This is most clearly demonstrated through the neutralising effect of basic protamine,[9, 10] which instantaneously neutralises the action of heparin on the blood. The multiple effect of heparin on thromboplastin, prothrombin,[11, 12] thrombin,[13] the hæmolytic complement,[14] iso-hæmagglutinins and different enzymes is most easily explained as a loading and unloading of electric charges on the proteins concerned. In fact, the few synthetic organic chemicals we have, acting directly as anticoagulants, are sulphonic [15] or sulphuric esters [16, 17] of high molecular compounds. Nature has applied the same principles of synthesis and has done it in an excellent way, the product heparin being highly active and non-toxic. It would certainly not have introduced 45 per cent. of sulphuric acid into a polysaccharide without some useful purpose.

At a time when the sulphur content of heparin was denied by several authors, it was possible to demonstrate that it gives an exceedingly strong violet metachromatic reaction with toluidine blue,[18] a reaction which a Belgian histologist, Lison, had shown in 1933 to be given only by high molecular sulphuric esters. By means of this reaction we were able to demonstrate that heparin is produced by the mast cells.[19, 20] When Ehrlich, about sixty-five years ago, separated these cells from Waldemeyer's plasma cells, using methyl violet as the specific stain, he could hardly anticipate that his specific stain, in this case the toluidine blue, in due time would help us to demonstrate the natural anticoagulant at the site of its formation. A few years before the discovery of this connexion, Quensel,[21] a Swedish pathologist, had stated that the mast cells were unicellular glands of the connective tissue which must have some function in connexion with the blood. Now we know this function, even if we do not know to what extent heparin participates in keeping the blood fluid. The term heparinocytes [22] has recently been suggested as a convenient name for these cells, which form a fairly well-defined hormonal system.

As soon as heparin was obtained in a pure state in 1935, its use against thrombosis was taken up in Toronto and in Stockholm. During 1937-40, Crafoord in Stockholm,[23, 24, 25] Murray and co-workers in Toronto,[26, 27, 28] and others (Wetterdal [29] and Leissner [30] in Sweden) showed that thrombosis can be prevented in man by regular heparinisation. The most successful results were reported by Murray,[27, 31, 32, 33] who used it in vascular surgery. At an early date he and his co-workers also succeeded in treating acute thrombo-phlebitis and pulmonary embolism successfully with heparin. The first results obtained in Sweden with heparin in acute thrombosis and pulmonary embolism were summarised in a symposium on heparin and thrombosis in November 1940.[34] In Sweden regular treatment with heparin of all cases of thrombosis and pulmonary embolism was taken up by Bauer [34] at the Mariestad Hospital in 1940. At several clinics in Stockholm, especially those of Crafoord and of Wetterdal of Sabbatsberg and of Lundqvist at Sodersjukhuset, as well as at various provincial hospitals, this therapy has now been in use for the past three or four years.

The introduction of dicumarol to Sweden by Lehmann in 1942 further resulted in a wide application of this anticoagulant in the treatment of thrombosis. The experience acquired in Sweden in using heparin against thrombosis can already be considered as quite sufficient, and the number of patients treated with dicumarol is steadily increasing. The beneficial influence of both these drugs has been amply demonstrated. The results will be briefly summarised.

The Course of Thrombosis in Untreated Cases.—Let us first discuss the historical background against which the modern treatment is to be considered. The mortality among the thrombotic cases is to be seen from Table I.

In the surgical series pulmonary embolism occurred in 50-60 per cent. of the cases and fatal embolism in about 20 per cent. of them. In the obstetric series the corresponding figures are lower, the mortality being only 3·5-5 per cent. The fact that the mortality was the same —20 per cent.—at the great German and Austrian hospitals at the beginning of this century, as it was at the Mayo Clinic during the thirteen years preceding 1940, cannot be attributed to chance alone. Independent of time and space, thrombotic disease has its definite character. Thus, before heparin, in surgical clinics, of every five patients suffering from thrombosis one died.

TABLE I

The Frequency of (a) Pulmonary Embolism, and of (b) Deaths from Pulmonary Embolism, in Cases of Thrombosis, from the Large Statistical Series in the Literature

Authors.	No. of Cases of Thrombosis.	Pulmonary Embolism.		Fatal Pulmonary Embolism.		
		No. of Cases.	Percentage.	No. of Cases.	Percentage of Total Cases of Thrombosis.	Percentage of Cases of Pulmonary Embolism.
Surgical Cases :						
Scheidegg, Singer, Braun, Ranzi	1550	746	48·1	298	19·2	40·0
Barker, Nygaard, Walters, Priestly	1665	897	53·8	343	20·6	38·5
Linde, Nicolaysen, Dahl-Iverson, Ramberg	1230	740	60·1	166	15·5	24·4
Obstetrical Cases :						
Holzmann, Mikuliz-Radecki, Braun	749	119	15·8	26	3·47	21·9
Hellsten	420	150	35·8	20	4·76	13·3

Previously the occurrence of deep venous thrombosis prolonged the hospital stay by, on an average, 5-6 weeks. This statement is based partly on older statistics published by Nettelblad[35] (1931) in Sweden, Schaanning[36] (1924) in Norway, and Dahl-Iversen and Ramberg[37] (1932) in Denmark, and partly on recent statistics examined by Linde[38] (1941), Hellsten[39] (1943), and Zilliaeus[40] (1946), all three from Sweden.

The third feature of importance for the individual as well as for the community in general concerns the post-thrombotic sequelæ.

The after-effects of thrombotic disease are of primary importance because of the serious inconvenience they cause. In most of the cases thrombosis in the veins of the leg is the cause of the disabling indurations and ulcers in the legs. This matter will be treated in greater detail later.

Anticoagulant Therapy.—I turn now to the results obtained in these hospitals in Sweden in which specific therapy has been introduced and regularly carried out. The results achieved by Bauer[41] at the Mariestad Hospital will first be examined. At this hospital all cases of deep venous thrombosis or pulmonary embolism occurring after

1st October 1940 have been regularly treated with heparin. In other words, the cases were diagnosed as early as possible, if necessary by means of venography; heparin treatment was instituted with doses of 350-450 mg. daily, early movement therapy was applied and the patients made to get up as soon as possible. The results will be seen in Table II.

In the conservatively treated cases the mortality rate, as previously mentioned, is about 20 per cent.—18 per cent. in this series. The corresponding figure for the patients treated with heparin is 1·4 per cent.—three cases.* During the second (later) period 79 patients

TABLE II

Comparison between Conservative (1929-38) and Heparin (1940-45) Treatment of Thrombosis

Treatment.	Total No. of Patients.	No. of Cases of Thrombosis.	Fatal Pulmonary Embolism.		Average Duration of Stay in Bed. (Days)	Post-Thrombotic Sequelæ.
			No. of Cases.	Percentage of Cases of Thrombosis.		
1929-1938 Conservative . .	25,628	264	47	18·0	40·0	Serious
1940-1945 Heparin . .	16,495	209	3	1·4	4·7	None or very slight

were already suffering from thrombosis when they came to the hospital, and could therefore not receive regular early abortive treatment. After 7500 operations in these five years there were no sudden deaths from pulmonary embolism. In the earlier period at the same hospital, 4-5 cases of fatal pulmonary embolism had occurred every year. As to the sequelæ following venous thrombosis in the leg, there was a marked difference between the two groups. The practical details as to the early diagnosis, the technique of venography, and heparin treatment are to be found in papers by Hellsten [42] and by Bauer.[43, 44, 45, 46]

A similar striking difference can be observed when the results at some clinics in Stockholm are analysed. Thus in 1940 and 1941, in the Medical Ward of Karolinska Sjukhuset, 9 died out of 16 non-treated cases. Heparin treatment was introduced in 1942, and in 1943 and 1944 heparin was given in conjunction with dicumarol; in these years 22 cases of deep venous thrombosis occurred, without any death. Linde [47] studied the cases of thrombosis occurring in the last two of these years in some surgical clinics where anticoagulants were not used. In one of the clinics, 17 deaths occurred in 71 cases, 9 as a result of sudden pulmonary embolism. In another clinic 5 died out of 41 non-treated patients; whereas 26 cases treated with

* For various reasons none of these three cases could be treated in the regular way with heparin. One was a case of superficial thrombo-phlebitis, which suddenly progressed to the deep veins and resulted in fatal embolism.

heparin or dicumarol all survived. During this period, at Sabbatsberg Hospital, Crafoord treated 38 patients and Wetterdal 36 patients without any fatal complications.

Stimulated by these results, Zilliacus [40] has recently made a study of the cases of thrombosis for the past five years from 19 Swedish clinics, most of them in Stockholm, where heparin and dicumarol have been in use at least during the last three years. The material is derived from eight surgical, seven obstetric and gynæcological, and four medical departments. The distribution among the various groups and the incidence figures for thrombosis and pulmonary embolism are shown in Table III.

TABLE III

The Frequency of Thrombosis and Embolism after Surgical Operations, Childbirth, Gynæcological Operations, and in Medical Cases (Zilliacus, 19 Swedish Clinics, 1940-45)

Cases.	Thrombo-embolic Cases.		Pulmonary Embolism.			Fatal Pulmonary Embolism.				No. of Follow-up Examinations.
	No.	Percentage of Total Cases.	No.	Percentage of Thrombotic Cases.	Total Cases.	No.	Percentage of Thrombo-embolic Cases.	Embolic Cases.	Total Cases.	
Surgical . . 125,524	646	0·51	284	43·0	0·22	132	20·2	46·1	0·103	387
Obstetric-gynæcological . 96,672	387	0·40	85	21·9	0·08	11	2·8	12·9	0·011	318
Medical . . 34,086	125	0·37	39	31·2	0·114	18	15·2	48·6	0·056	60
Totals . . 256,282	1158		408			161*				765

* Out of the 161 cases of fatal pulmonary embolism, 135 occurred without other signs of thrombosis, and 26 after previous signs of thrombosis.

Zilliacus has arranged the cases into groups according to the method of treatment applied : (1) conservative treatment, (2) treatment with heparin alone, (3) treatment with heparin and dicumarol and (4) treatment with dicumarol alone. In the last three groups active movements in bed were prescribed, and the patients were soon out of bed.

The influence of specific treatment on the period of confinement to bed and on the temperature will be seen from Table IV.

Thus in the conservatively treated cases, the average time required for treatment, counted from the appearance of thrombosis, was 36 days or more than 5 weeks, and the temperature was elevated for 23 days. For all specifically treated groups the recumbency time was from 8 to 10 days and the temperature was elevated for 6·4-10 days. The influence of specific treatment on the body temperature seems to be the best indication of its action.

TABLE IV

Stay in Bed and Rise in Temperature in 790 Cases of Deep Venous Thrombosis given no Specific Treatment, or Treated with Heparin, with Heparin and Dicumarol, or with Dicumarol Alone

Treatment.	Site.	No. of Cases of Thrombosis (excluding Sudden Pulmonary Embolism Alone).	Time from Appearance of Thrombotic Symptoms to Patient getting up. Days (mean)	Duration of Fever after Appearance of Signs of Thrombosis. Days (mean)
No specific treatment	Calf . . .	43 ⎱ 214	35·1	21·0
	Thigh, or calf and thigh . .	171 ⎰		
Heparin	Calf . . .	155	8·7	6·9
	Thigh, or calf and thigh . .	187	11·1	8·7
Heparin and Dicumarol	Calf . . .	40 ⎱ 576	8·3	7·3
	Thigh, or calf and thigh . .	63	10·5	7·6
Dicumarol	Calf . . .	71	8·2	7·5
	Thigh, or calf and thigh . .	60 ⎰	11·3	8·8
	Total . .	790		

The incidence of complicating pulmonary embolism and spread to the other leg will be seen from Table V.

TABLE V

Pulmonary Embolism; Spread to the Second Leg; Progression; and Post-Thrombotic Sequelæ in 790 Cases of Deep Venous Thrombosis given no Specific Treatment, or Treated with Heparin, with Heparin and Dicumarol, or with Dicumarol Alone

Treatment.	Site.	No. of Cases of Thrombosis (excluding Sudden Pulmonary Embolism Alone).	No. of Cases of Pulmonary Embolism Complicating Thrombotic Process.				Cases in which Thrombosis Spread to Other Leg.	Follow-up Examination. No. of Cases.	Index of Sequelæ. (mean)
			During Active Thrombosis.	Before Active Thrombosis.	After Active Thrombosis.	Fatal Cases.			
No specific treatment	Calf . .	43 ⎱ 214	60	8	5	20	66	132	5·0
	Thigh, or calf and thigh	171 ⎰							
Heparin	Calf . .	155	2 (+1 before treatment begun)	5	4	2	2 (+1 recurrence in same leg)	130	2·2
	Thigh, or calf and thigh	187	4 (+3 before treatment begun)	8	2 (2nd after treatment)	...	3 (+4 after treatment +1 recurrence in same leg)	154	4·5
Heparin and Dicumarol	Calf . .	40 ⎱ 576	...	1	...	...	1 after treatment	32	2·5
	Thigh, or calf and thigh	63	3 (before treatment begun)	4	...	...	2	47	4·0
Dicumarol	Calf . .	71	1 (before treatment begun)	2	...	...	1	62	2·5
	Thigh, or calf and thigh	60 ⎰	2 (+2 before treatment begun)	...	...	1	...	44	5·5
Totals .		790				23		601	

Of 214 conservatively treated cases, 20 patients, or 9·4 per cent., died, while among 576 specifically treated cases only 3 cases had a

fatal outcome, 2 of them 8-12 days after setting out the heparin treatment, an insignificant mortality. If early and late attacks of embolism occurring before the start and after the finish of the treatment are also included, pulmonary embolism occurred in 34 per cent. of the conservatively treated cases and in 7·6 per cent. of the patients given specific treatment. Only 1·4 per cent. of the patients in the last group showed an embolism during the course of the treatment, and only one patient died.

It will further be seen that the thrombosis progressed to the other leg in 31 per cent. of the patients in the conservatively treated group, but in only 2·2 per cent. of the cases receiving anticoagulants. What this means in the avoidance of post-thrombotic discomforts is evident.

Besides these 790 cases of deep venous thrombosis, the material included 280 cases of sudden pulmonary embolism without other signs of thrombosis. These were arranged in three groups : (1) immediately fatal cases, 114 ; (2) conservatively treated cases, 63 ; (3) cases treated with heparin or dicumarol, 103. As regards group 1, it can be mentioned that at the post-mortem examination newly formed thrombi were found in deep veins of the leg in not less than 60 cases, while in 26 cases these veins were not examined. Many of these cases could certainly have been diagnosed and the patients saved. Nineteen out of the 63 conservatively treated patients in group 2 died, some of them after repeated attacks. None of the 103 patients in group 3 died. Seventy-one were treated with heparin and 16 with heparin in conjunction with dicumarol.

As to the influence of specific treatment on the sequelæ following thrombosis in the leg, the material of Bauer and of Zilliacus gives satisfactory information. During the first three years, 1st October 1940 to 30th September 1943, 127 cases of thrombosis were treated with heparin at Mariestad. Of these patients, 15 died in the following years, while 9 patients could either not be found, or were for some reason unsuitable for re-examination. The data on the sequelæ in the 103 cases examined at the follow-up examination will be found in Table VI.

TABLE VI

Post-Thrombotic Sequelæ after 2-5 Years in 103 Cases of Deep Venous Thrombosis Receiving Regular Heparin Treatment at the Mariestad Hospital during 1940-43 (Bauer).

Site of Thrombosis.	Leg Normal.	Swelling of the Leg.				Heaviness and Pains.	
		Calf.			Thigh.	Moderate.	Severe.
		Mild.	Moderate.	Severe.			
Calf (76 cases) . . .	60 (80 per cent.)	16	...	...	...	2	...
Thigh (27 cases) . .	14 (50 per cent.)	3	8	2	5	...	3

Thus in the 76 cases in which the popliteal vein had been saved, 60 suffered from no discomfort whatsoever, and 16 showed an insignificant swelling in the calf only. Of the 27 cases in which the thrombosing process had reached the popliteal vein before treatment with heparin was begun, 14 cases only were quite without discomfort. The remaining 13 had symptoms in the leg. All suffered from swelling of the lower part of the leg, in most instances moderate to severe. Five had in addition swelling of the thigh, 3 had severe pain and a feeling of heaviness in the leg.

Bauer [48] claimed that thrombosis in the deep veins of the thigh is practically always followed by post-thrombotic discomfort, usually of a severe kind, and Zilliacus [40] confirmed this view. He assessed the sequelæ in a numerical scale ranging from no discomfort at all (1), over subjective discomfort (2), and chronic swelling of the lower leg (4), to ulcers and chronic swelling of the lower thigh (6 to 8). His results are shown in Table V. Among the 214 conservatively treated cases the thrombosing process had progressed to the thigh in 160 cases, i.e. 80 per cent., while the corresponding figure for the specifically treated cases was 55 per cent., or 310 cases out of 576. As soon as the thrombosis involves the thigh, the sequelæ are aggravated because of the destruction of the deep venous channel in the thigh (index about 4·3-5·0) irrespective of whether specific therapy has been given or not. When the process has been confined to the calf, after-effects are either avoided, or are insignificant (mean index 2·5). Zilliacus found that the sequelæ are already almost fully developed one year after the acute stage.

If Bauer's material is compared with that of Zilliacus, the importance of early diagnosis, followed by immediate heparin treatment, will be clearly evident. At Bauer's clinic, where all cases except the 79 with thrombosis diagnosed before their arrival at the hospital received early heparin treatment, the process did not progress beyond the calf in 80 per cent. of the cases. From Zilliacus's data on conservatively treated cases, it will be seen that thrombosis progressed to the thigh in 80 per cent. of the cases. In his remaining material, where the cases presumably were not treated in the best way with respect to early diagnosis and therapy, the process progressed to the thigh, in spite of the specific therapy, in 55 per cent. of the cases. Seeing that obliteration of the popliteal vein or the deep femoral vein, or of both, must at all costs be prevented, the necessity of early diagnosis and early effective heparin therapy is evident.

Similar results in treating acute thrombo-phlebitis with heparin were reported by Murray and MacKenzie [49] in 1942. Among 218 thrombotic cases there were no deaths and not even any new pulmonary emboli, although 63 of the patients had attacks of pulmonary embolism before the treatment was started.

DICUMAROL

When Morawitz[50] in 1934 summarised the therapeutic possibilities for influencing the course of the thrombotic diseases, he deplored the fact that heparin was so expensive, germanin so toxic, and hirudin both. He then suggested another way of approaching the solution of the problem. The same result could possibly be obtained if we could find an agent causing a mild, harmless impairment of the liver function, eliminating prothrombin and fibrinogen production without causing irreparable hepatic damage like that in chloroform poisoning. Dicumarol, the agent causing " sweet clover disease " in cattle, exactly fulfils these requirements. In moderate doses it eliminates prothrombin production and influences the fibrinogen content of the blood, in excessive doses it causes necrosis of the liver cells. It has already been used quite extensively in the prophylaxis and treatment of thrombosis.

The hæmorrhagic agent in " sweet clover disease " discovered by Schofield[53] in Canada in 1922 was isolated, chemically identified and synthesised by Link[54] and his associates at the Wisconsin Agricultural Experiment Station in 1940-41. Its physiological action has been dealt with in several papers.[51, 52, 54, 55, 56, 57, 58] As to its clinical application, the papers have so far dealt mainly with its use as a prophylactic against thrombosis. Lehmann[59, 60, 61] in Sweden has made consistent use of it; Bruzelius,[62] at Lund, has given dicumarol prophylactically after operations in about 1500 cases.

At the Mayo Clinic, Barker[63] and his associates reported on 1000 surgical patients who were given dicumarol post-operatively. Of these patients, 379 had earlier had thrombosis or pulmonary embolism, and on 438 of them abdominal hysterectomy had been performed. In a previous series from the Mayo Clinic comprising 678 cases with non-fatal pulmonary embolism subsequent thrombosis had occurred in 43·8 per cent. and fatal pulmonary embolism in 8·3 per cent. In this later series 180 such cases were treated with dicumarol. Only two of them developed pulmonary embolism and one died, an inadequately treated case. Of 897 patients from the earlier series with thrombo-phlebitis, 10·6 per cent. had subsequent thrombosis and 5·7 per cent. died of pulmonary embolism. Of 138 similar patients in the later series, only 4 had a recurrence of the symptoms and none died. A very remarkable fact was that embolism did not occur in the 438 patients on whom abdominal hysterectomy had been performed, although a frequency of 4 per cent. for post-operative thrombo-phlebitis and 0·7 per cent. for fatal pulmonary embolism was expected in these cases. Minor bleedings occurred in 3·9 per cent. of the cases and major hæmorrhages in 2·5 per cent.

Zilliacus reported on 131 thrombotic cases treated with dicumarol and on 103 cases treated with heparin in conjunction with dicumarol. The results were good. Details as to the treatment with dicumarol are to be found in papers by Jansen,[52] Lehmann,[61] Barker et al.[63] and Bruzelius.[62]

These facts concerning the use of heparin in Sweden and in Canada as supplemented by the findings in conjunction with dicumarol justify the statement that the most usual forms of thrombosis can now be effectively combated. With early diagnosis and regular treatment with anticoagulants, there is practically no mortality from diagnosed, uncomplicated thrombosis of the leg or from pulmonary embolism which is not instantaneously fatal. Failure to prevent death or spread of the process to the thigh or to the other leg may in most, if not in all, cases be attributed either to neglected diagnosis or to defective treatment. The low mortality, 5·9 per cent., among the thrombotic cases in Sweden, as reported to the State Medical Board in 1944, seems to have a connexion with the treatment; the previous figure having been about 9 per cent.

Now the question arises whether similar results could be obtained by other means, such as active movements and early getting up, sympathetic block causing vasodilatation in the leg, and surgical ligation of the larger veins. Evidently all these measures are likely to shorten the length of the stay in hospital; they are all highly recommended by different authors.

It is evident that medical gymnastics and early getting up of patients can reduce the incidence of thrombo-embolism. Thus Hermansson [64] and Mortens [65] have reduced the incidence in the obstetric series to half the original figure, Mortens from 2·27 to 1·65 per cent. The favourable influence of early getting up on the post-operative state in general has been stressed by many authors,[66, 67] particularly because of the low incidence of thrombosis.[68, 69] However, it is admitted by several authors that these measures do not provide full security against the development of thrombo-phlebitis. They are evidently still less reliable as therapeutic agents in the case of an acute deep venous thrombosis or pulmonary embolism. This is most clearly demonstrated by the mortality rate among the thrombotic cases, which has not decreased although the possible use of gymnastics has been known since the days of Hippocrates. The figure, 20 per cent., was the same at the beginning of this century in Germany and Austria as it was recently at the Mayo Clinic in the U.S.A.—15-30 per cent. The same figures were also found in a number of recent Swedish statistical series. In fact, the older clinicians like Morawitz made serious efforts to use movement therapy, but *belehrt durch manche Rückschläge* had to give it up because of the risk of pulmonary embolism which was associated with it. Instead of the novocaine block of the lumbar ganglia suggested by Leriche and by Ochsner, venous ligation, with or without thrombectomy, has been preferred by the most recent workers. It has been applied in fairly large series of patients (Fine,[70] Homans,[71] Allen,[72] Veal [73] and Buxton [74]). Even in the selected cases, however, in which such rather unphysiological surgical interventions may be considered as indicated, anticoagulant therapy could be of value in order to check further thrombosis in the operative field.

SOCIAL ASPECTS OF THROMBO-EMBOLISM

Early diagnosis of thrombosis in the legs, or of a pulmonary embolism, followed by regular treatment with anticoagulants, has now become an urgent necessity for the physician, not only in order to save the patient's health but also on purely social grounds. Therefore a short outline may be given of the social significance of this disease.

Incidence of Thrombo-embolism.—Thrombo-embolic complications will occur in hospital patients in at least 0·5-1 per cent. of the cases, under certain circumstances in a still higher percentage. In larger surgical series the figures are between 0·7 and 3·4 per cent., and in obstetric series between 0·6 and 2·1 per cent. In medical clinics similar figures are obtained, the difference, however, being that thrombosis in the leg and pulmonary embolism preponderate in the previous series, whereas coronary and cerebral thrombosis are fairly common in medical wards. In surgical clinics where careful attention is paid to the prophylaxis by means of active movements and early getting up, the figure can be kept as low as 0·7 per cent., as was found at four surgical clinics in Sweden during the past decade. A similar result has also been obtained at obstetric clinics (Mortens[65]) by the same means. Thus a certain number of thrombotic complications is always to be encountered ; under ordinary conditions about one per cent. of all patients treated in surgical and medical wards and at maternity hospitals. A lower figure, one in 200 patients, could possibly be attained under the best circumstances. In Sweden, where there are at least 5000 thrombotic cases a year in a population of 6·3 millions, 0·8 per cent. of the patients admitted to hospital in 1940 and 0·8 per 1000 of the whole population developed deep venous thrombosis or pulmonary embolism.

As to the mortality in thrombo-embolism, it was conclusively shown by Robertson[75] in 1928 that during the preceding twenty years one patient out of 400 operated upon died of pulmonary embolism, a statement based on material comprising more than 2 million operations.

The mortality rate, 15-20 per cent. of the thrombotic cases in surgical series and 3·5 per cent. in obstetric cases, has already been discussed (Table I).

Elimination of the mortality in this disease, at least among people of not too high an age, would evidently mean a great saving of human lives. The experience so far obtained points to the fact that such an elimination is possible. If regular treatment with heparin, or, if possible, with dicumarol, is given, pulmonary emboli do not develop, or at least no serious ones.

The mortality in thrombo-embolism could further be greatly reduced through a more careful observation of the earliest signs of thrombosis. Thus thrombosis in the leg had not been observed in 124 out of 157 cases (80 per cent.) of the fatal cases reported by Zilliacus.[40] On the other hand, fatal casualties are rare in clinics

where due attention is paid to early diagnosis. It should further be kept in mind that pneumonic processes very often are nothing but the result of pulmonary emboli arising from latent, non-diagnosed thrombi.

As regards the length of stay in hospital, there is a very striking difference between the older series, and the new ones in which anti-coagulant therapy has been given. As has been pointed out, thrombotic cases were earlier cared for for 5-6 weeks or more. Now the stay in hospital ranges from 7 to 12 days (Zilliacus [40]). In the best controlled clinics (Bauer [41]) the stay in bed lasts only 5 days after the thrombosis has been diagnosed. When anticoagulant therapy is used the time in hospital is shortened by about one month.

Not the least important are the results obtained with respect to post-thrombotic sequelæ. It has lately been established that venous thrombosis gives rise to disabling indurations and ulcers of the lower leg. The earlier literature contained little about the connexion between leg ulcers and thrombo-phlebitis; at present such a connexion is recognised (Homans,[76] 1938; Leriche,[77] 1938). It is now established that chronic indurations and ulcers of the leg very often follow thrombo-phlebitic processes in the deep veins of the leg, in the vena poplitea and the vena femoralis (Homans,[78] 1939). Thrombosis has been shown to be the most important etiological factor in leg ulcers. Thus among 432 patients with leg ulcers, Birger [79] (1941) found thrombo-phlebitic symptoms in the earlier history in 60 per cent. of the cases. Bauer [48] (1942), basing his diagnosis on venographic studies of the veins, found earlier thrombosis of the deep veins of the thigh to be the cause of indurations and ulcers in 33 out of 38 non-specific cases (87 per cent.).

The efficacy of early diagnosis and early heparin treatment in restricting the process to the lower leg has been amply demonstrated by Bauer [41] and by Zilliacus.[40] By this means it is possible to prevent a considerable number of thrombotic patients from developing subsequent disabling ulcers and indurations in one or both legs.

In addition to pains and discomfort for the patient, disabling leg ulcers cause a considerable cost to the community. Thus Roholm [80] found that in Denmark there occur at least 5000 cases annually, causing in 1935, for example, a cost to the State of two million Danish crowns (£100,000), when the hospital expenses, the lost working days and the life annuities were added together.

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MENINGOCOCCÆMIA

PART III. BACTERIOLOGY, SEROLOGY AND ÆTIOLOGY

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In the first paper 3 cases of chronic meningococcæmia were described, with a historical review, and these and other 259 published cases were reviewed in the second paper from the clinical point of view. The present paper deals with the cases with regard to bacteriology, serology and ætiology. An attempt is made to discover from the available evidence (1) why in these cases the organism should produce meningococcæmia rather than meningitis, (2) where the organism resides in the body between attacks, and (3) the cause of the intermittency of the condition. With regard to the first question the points requiring investigation are: any evidence as to a different portal of entry, a comparison of the serological type of the infecting organism in meningococcæmia as compared with that in meningitis, any evidence as to relative virulence, and as to the state of susceptibility of individuals and community.

It is necessary first to discuss certain details as to infection in cerebrospinal meningitis.

MODE OF INFECTION IN MENINGOCOCCAL MENINGITIS, AND EPIDEMIOLOGY

That the primary infection is of the nasopharynx, and that the disease is spread almost entirely by carriers, and practically not at all by cases of meningitis are facts almost universally accepted. There is not, however, complete agreement that the infection of the nasopharynx produces a demonstrable local inflammation, and it is evident that epidemics differ in this respect. In some, meningitis is preceded in almost every case by catarrh, while in others this is almost entirely absent. It is evident also that as catarrhal conditions and cerebrospinal meningitis have the same seasonal prevalence, the presence of catarrhal conditions due mainly to other organisms will help to produce epidemics of cerebrospinal meningitis through increased coughing and sneezing.

There is no doubt that epidemics of cerebrospinal meningitis are in fact epidemics of meningococcal nasopharyngeal infection of which only a small percentage develop meningitis as Arkwright pointed out in 1915. Dopter (1918) wrote that there are not epidemics of cerebrospinal meningitis, but rather epidemics of rhinopharyngitis, complicated sometimes by cerebrospinal meningitis. Other observers have described

epidemic meningitis in similar terms, but usually making use of the term " carriers " where Dopter speaks of cases of rhinopharyngitis.

It was believed in the last war (War Office Memorandum, 1917) that when the carrier rate reached 20 per cent. an epidemic of meningitis usually followed, and this figure was accepted for some time. But Dudley and Brennan (1934) showed that sometimes there were cases of meningitis when the carrier rate was as little as 5 per cent., while there might be no cases with a carrier rate as high as 54 per cent. of the local population. These figures suggest that the production of epidemics is determined more by an increased virulence of the organism than by the number of carriers, and it is also evident from recent experience that a relative increase of Group I meningococcus is an indication that an epidemic is about to take place. It is accepted that carriers do not often become cases of cerebrospinal meningitis. That is, if meningitis supervenes, it does so after only a brief naso-pharyngeal infection.

ROUTE OF INFECTION OF THE MENINGES : DIRECT SPREAD OR BY THE BLOOD STREAM ?

Much has been written on this controversy and it need only be briefly summarised here. Weigert and Weichselbaum's post-mortem findings led them to suggest that there was direct spread from the nasopharynx to the base of the brain. Westenhoeffer (1905) held for a time that infection of the brain took place through the sphenoidal sinus, but later experience led him to abandon this view. Other routes, more or less direct, were suggested, but the controversy came to be in the main as to whether infection took place along the lymphatics round the olfactory nerves, or by the blood stream.

Fronz (1897) found gram-negative diplococci in the ankle-joint of a child suffering from cerebrospinal meningitis, thus affording indirect evidence of blood spread. G. F. Still (1898) cultivated the organism during life from the tendon sheath of a finger-joint in a child suffering from posterior basic meningitis, and concluded that the organism might be found in the blood during life. This was done for the first time in a case of Osler's (1898) by Gwyn (1899). In 1903 Warfield and Walker published the first case of meningococcal endo-carditis. In the following years there were scattered cases in which meningococci were obtained from the blood stream in cerebrospinal meningitis, including two published by Schottmüller (1905), while another case of endocarditis was reported by Weichselbaum and Ghon (1905). Follet and Sacquépée (1906), describing two cases of meningococcal septicæmia, emphasised that in their opinion cerebro-spinal meningitis was a meningococcal septicæmia with, as point of entry, the pharynx, tonsil, nose or respiratory passages, and expressed with astonishing accuracy the now usually accepted views as to the nature of meningococcal infection. They were, however, much ahead

of their time. The dramatic and often terrible nature of cerebrospinal meningitis made it for long almost synonymous with meningococcal infection, which it most certainly is not. Herrick (1918a, 1918b, 1918c) was, at the end of the last war, one of the most active advocates of the view that the disease is not a primary meningitis, but a meningococcic sepsis with a secondary meningococcal localisation. He claimed that meningococci might be grown from the blood in 50 to 80 per cent. of all cases of epidemic meningococcus infection, and that the average duration of the septicæmic phase prior to infection of the meninges was forty-eight hours. Others have written to the same effect. Carnegie Dickson (1917), by post-mortem examinations in fatal cases, showed that there was infection of the ventricles. Experimental work, usually with monkeys and rabbits, has shown that meningitis could be produced, under certain conditions, by blood invasion, and recently Buddingh and Polk (1939) have shown that infection of the meninges can be produced in chick embryos *via* the nasopharynx and blood stream.

It seems to be the view of those who are still loath to accept the condition as primarily septicæmic that while septicæmia occurs it follows the meningeal infection. It is very difficult to bring proof as to this point in the human being. All cases in which blood infection of a few days or more precedes the onset of meningitis are regarded as atypical infections, and in the typical meningitis both meningeal and blood infection occur so quickly that it is extremely difficult to bring absolute proof as to which occurred first. There is now, however, a very great amount of evidence that the invasion of the blood stream is primary.

The view of the majority is, at present, that meningococcal meningitis occurs as a result of invasion of the blood stream *via* the lymphatics from the nasopharynx, and that the primary site of involvement in the central nervous system is the lateral ventricles by way of the choroid plexuses.

PORTAL OF ENTRY IN MENINGOCOCCÆMIA

It has always been assumed that the portal of entry is the same in meningococcæmia as in meningitis : that is, the nasopharynx. It was recorded in the first paper that 22 per cent. of the cases had sore throat immediately before the illness or during the first few days. In two series of cases in epidemic periods the majority had sore throats prior to the illness ; but in other epidemic series there was no initial sore throat, and most of the sporadic cases had not sore throat. This corresponds with the varying incidence of sore throat in cerebrospinal meningitis.

When we look next for bacteriological proof of the presence of the meningococcus in the nasopharynx prior to or early in the illness it is found that there is no evidence one way or the other. Forty-seven of the cases of meningococcæmia were tested by bacteriological examina-

tion of nasopharyngeal swabs, but four of these were negative routine examinations made prior to discharge from hospital. Of the remaining 43 cases in which examinations are recorded (probably others were made with negative results and not mentioned), none were examined prior to the onset of illness, and the great majority of the cultures were made, usually after admission of the patient to hospital, at a varying and sometimes unstated period after the onset of illness.

It can only be said therefore that it is the assumption that the portal of entry is the same in meningococcæmia as in meningitis, but no bacteriological proof is available.

SEROLOGICAL TYPES OF MENINGOCOCCI

There was for a time considerable confusion as to the serological types of meningococci owing to workers in different countries, and even in the same country, conducting independent researches and using a different terminology. In France, Dopter in 1909, and Dopter and Pauron in 1914, divided what we now call meningococci into " the meningococcus " and " parameningococci." The organism which they termed the meningococcus was the then prevailing cause of epidemic cerebrospinal meningitis, now known as Group I meningo-coccus. As a result of work done during and after the 1914-1918 war—chiefly by Ellis, Arkwright, Gordon and Murray, Nicolle Debains and Jouan, and Griffiths—meningococci have been divided into two groups, I and II, the former composed of two closely allied types, 1 and 3, the latter of two similarly closely allied types, 2 and 4. Gordon and Murray were responsible for the subdivision of groups by absorption tests. Group I meningococcus is the " meningococcus " of Dopter, and Type A of Nicolle. Group II is the alpha-parameningococcus of Dopter, and Type B of Nicolle. The exact identity of parameningococci β and γ of Dopter, and meningococci Types C and D of Nicolle, Debains and Jouans is not now known.

Groups I and II meningococci have been the prevailing varieties in the United States and South America as well as in Britain and France. It is not known whether the types prevailing in Germany during the 1914-1918 war were identical, and it does not even now seem to be known how the types prevalent in Germany in the inter-war period compared with Groups I and II. In Denmark, Thomsen (1925) and Wulf found that the meningococcus responsible for the epidemic of cerebrospinal meningitis of 1917 to 1920 was quite different from the British types 1, 2, 3, and 4, and therefore from the French types A and B. It was also termed Type A, to which we may add (Danish) to differentiate it from the French Type A.

In France, typing sera, either Dopter's or Nicolle's, were available during the 1914-1918 war and after. In Britain, sera prepared on the basis of Gordon and Murray's classification of four types were available during that war and for some time after. In America, Gordon's sera

seem to have been available to some workers at the end of that war, but most of the identification of meningococci was made with the polyvalent sera used for treatment. In the inter-war period when there were no major epidemics it was difficult to obtain typing sera in Britain, but in recent years sera of Group I and Group II have been available once more, while separation of the types within these groups has usually been carried out by special laboratories.

It is perhaps not generally realised, except by those working with these organisms, how close is the antigenic relationship between the various types. There is antigenic overlapping, that is, there are antigens common to both groups of meningococci and even to other members of the Neisseria. Further there is difficulty in inter-epidemic periods in maintaining strains in their original serological purity. Branham (1940) says that the difficulty in preparing type sera in the States before the recent war was that the original Gordon type strains maintained in the laboratories had become degraded. Their antigens had " spread." Such rougher strains would tend to be richer in group antigens, and sera prepared with them would lack specificity. Further, it was shown by this worker and others that even the strains obtained fresh from epidemic cases had undergone change. Types 1 and 3, which they regard as the real epidemic types, were still very close together, both antigenically and chemically, and for all practical purposes were identical, but Types 2 and 4 had drifted apart, and were now much more distinct from each other serologically. In addition, Type 2 showed much more·variation antigenically and was not now the clear-cut type that it had formerly been. There was more variation between individual strains. Capsules are present in Group I organisms, and the specific antigenic factor is in the capsule, as it is in pneumococci. Capsules have been demonstrated so far only in one sub-type of Type 2 meningococcus. It had always been more difficult to prepare good sera against Group II than against Group I, and this difficulty seems to have increased before the recent war.

Branham (1940) and others regard Group I meningococcus as the " epidemic " strain, and hold the view that Group II is essentially the cause of sporadic cases of meningitis, and of the septicæmic type of infection. Apparently she refers to the acute septicæmic form of infection as there is no specific reference to chronic meningococcæmia. Netter (1917), noting that Group II meningococcus was replacing Group I as the predominant type in France during the 1914-1918 war, suggested that this change might be the cause of the greater frequency of acute septicæmic types of infection with purpura, of multiple arthritis, of iridocyclitis, and of meningococcæmia without meningitis. As regards the type causing epidemics it seems to be true that, so far as is known, the world epidemics of the last two wars have been primarily due to Group I meningococcus. It seems, however, to be going too far to class Group II as a non-epidemic variety, though perhaps Group II epidemics occur chiefly in the wake of epidemics

due to Group I, and Group II seems to have a greater tendency to endemicity than Group I. It may be that waning virulence of Group I and increasing immunity of the population to that variety may, if conditions favouring an epidemic are still present, result in a predominance of Group II infections. But the possibility of a mutation from one group to the other exists.

Types of Meningococci in Meningococcæmia

In analysing the cases it is assumed that Dopter's meningococcus, Nicolle's Type A and our own Group I are the same organism, and that Dopter's parameningococcus (usually) and Nicolle's Type B are our Group II. Strains agglutinated to a good titre by American polyvalent serum and called by the American bacteriologists " regular " or " normal " strains are considered in this review to be either Group I or II, probably the former where this was known to be the prevailing epidemic strain.

The meningococcus was typed in 126 of the 262 cases, but the 13 of Hill and Lever must be omitted as the type in each case of meningococcæmia was not specifically stated, although it is clear that they were, like their meningitic cases, predominantly Group I. Of the remaining 113 typed cases, 42 yielded Group I and 29 Group II. Of the Group I cases, 17 were described as Type 1, and 2 were proved to be Type 3. Of the Group II cases 8 were described as Type 2, and 3 were proved to be Type 4. The remainder were identified by group sera. There were in addition 18 strains which were probably Group I or Group II, and at any rate of the same variety as those causing meningitis in the same district; these include strains agglutinated to a good titre by stock and polyvalent sera, by " Wassermann " serum, by " Vienna " serum, and " regular " or " normal " American strains. Two strains were the French Type C, and 12 cases were shown by the complement fixation test to be the Danish Type A. Only 10 strains were types not commonly found in epidemic meningitis, including strains which were inagglutinable, or agglutinated by both sera, or described as " paranormal."

Cases of meningococcæmia occurring in epidemics of meningitis were usually due to the organism found in the meningitic cases, whether Group I or Group II. But both Group I and Group II cases of meningococcæmia also occurred in inter-epidemic periods. Most of the atypical strains came from sporadic cases, as do most of the atypical strains from the meninges.

There is therefore no evidence that the meningococci causing meningococcæmia differ serologically from those causing meningitis.

There is still the question: is it true that Group II has more tendency to cause bacteræmia without meningitis than Group I ? Or, conversely, that Group I has a greater tendency to infect the meninges than Group II ? The figures in the present series do not suggest that

this is the case, with 42 Group I cases against 29 due to Group II.   But for a definite answer it would be necessary to collect a large number of cases of pharyngeal infection by the meningococcus, and to ascertain what proportion of each group developed meningitis on the one hand, and septicæmia only on the other.   This might have been feasible when large numbers of contacts were being examined, but it is no longer so.

An examination of some of the epidemic series throws a little light on the question.   Daniels, Solomon and Jaquette (1943) had 80 cases of meningitis and, at the end of the same period, 32 of meningococcal bacteræmia without localisation in the meninges.   Of the 80 cases of meningitis, 62 were typed.   All were Type 1.   Of the 32 cases of meningococcæmia, 16 were typed ; 14 were Type 1, 1 Type 2, and 1 Type 2A.   That is, 100 per cent. of the cases of meningitis typed were Group I, and of the cases of meningococcæmia typed 87·5 per cent. were Group I, and 12·5 per cent. Group II.

Dingle, Thomas and Morton (1941) reported an epidemic of cerebrospinal meningitis in the city of Halifax (Canada) in the six months beginning August 1940.   Ninety-three cases were treated in hospital.   The epidemic strains were Group I.   It is not clear whether there were any meningitis cases due to Group II meningococcus, apart from one patient who was admitted in coma, but the only case of meningococcæmia during this Group I epidemic was a Group II infection.

There is therefore a small amount of evidence derived from these two epidemic series that in epidemics of Group I meningococcal meningitis small numbers of cases of meningococcæmia due to Group II meningococcus may occur.   But, in the main, cases of meningococcæmia occurring in epidemics of Group I cerebrospinal meningitis have been due to the prevalent Group I meningococcus. It is possible that in waning Group I epidemics, when Group II meningococcus may be increasing relatively, a greater proportion of cases of meningococcæmia occurs.   Some of the cases reported in France in the last war support this.   Ribierre, Hébert and Bloch (1919), for example, had 7 cases of meningococcæmia between September 1916 and March 1917 in the military hospital at Bar-le-Duc, where there were no other cases of this kind before or for some time after. Of 5 typed, 2 were Group I, 3 Group II.   The series of Daniels, Solomon and Jaquette referred to above is also interesting.   Between 1st January 1942 and 17th April 1943 they had 80 cases of meningitis and 32 of meningococcal bacteræmia without meningitis.   These 32 cases of meningococcæmia all occurred in the first four months of 1943, after the epidemic of meningitis had existed for a year.   It was really an epidemic of meningococcæmia following an epidemic of meningitis. This may be interpreted as due to a waning virulence of the Group I meningococcus combined with an increased immunity of the population, but there was only a small degree of replacement of Group I by Group II meningococcus.

These organisms are so closely related that it would only require a loss of the capsular antigen of Group I and a slight rearrangement of other antigens for Group I to become Group II. It is an obvious possibility that in a waning epidemic Group I might tend to be transformed into Group II. Against it is the fact that some epidemics are due to clear-cut Group II meningococci, and these are fully as virulent as Group I.

Copeman's series of 15 cases differed in that they were received in a military hospital between September 1941 and March 1942 and "meningitis was at no time epidemic in the areas from which these cases were derived." It is a notable feature of meningococcæmia that sporadic cases rarely infect contacts.

Acute septicæmic infection is not covered by the present review, and no evidence as to the alleged special tendency of Group II meningo-coccus to produce such conditions is therefore produced.

COMPARISON OF GROUP I AND GROUP II CASES OF MENINGOCOCCÆMIA

There were available for analysis 41 cases in which the organism was definitely proved to be Group I meningococcus and 29 similarly proved to be due to Group II.

As regards *mortality*, 2 of the Group I cases died, a mortality of 5 per cent., but if we eliminate the cases treated with sulphonamides, or presumably so treated—details are lacking in some of the later series—2 of 11 cases died : that is, 18 per cent. Both of these cases had terminal meningitis.

There were 5 deaths in the 29 Group II cases, but in 1 case death was due to chronic nephritis which had existed before the meningococcal infection, and in another it was due to anaphylaxis : this leaves 3 deaths in 29 cases, a mortality of 10 per cent. Again eliminating the cases treated with sulphonamides, there are 3 deaths, all with terminal meningitis, in 18 cases, a mortality of 16·6 per cent., compared with the mortality of 18 per cent. in the Group I cases.

That is, the mortality due to the meningococcus was practically the same in both groups.

The *average duration of illness* in Group I cases which recovered and in which sulphonamides were not used was eight-and-a-half weeks. In Group II cases, selected in the same way, and omitting 1 case in which there were infrequent attacks spread over a year (Lemierre and Piédelièvre, 1922), the average duration of illness was 14 weeks. Serum treatment was more adequately given in the Group I cases, and it is probable that the greater duration of illness in the Group II cases is in part due to the fact that divalent or poly-valent serum is often less potent against Group II than against Group I. This, however, is only part of the story, and it is evident from an examination of the case records that, contrary to views which

have been expressed, Group II meningococcæmia is often more severe and usually more intractable than that due to Group I. Brulé (1918) considered this to be so in French cases during the 1914-18 war.

There is no difference clinically between the two serological groups in their vulnerability to sulphonamides.

Virulence of the Organism

The next question is that of virulence. Is there any evidence that meningitis is caused by a meningococcus of high virulence, and chronic meningococcæmia by one of low virulence (with fulminating septicæmia due to a meningococcus of excessively high virulence)? This is possibly the case, combined of course with varying general or local susceptibility of the individual attacked, but no evidence is available. There are no comparable experiments in animals, which in any case do little more than estimate roughly the amount of endotoxin in a strain, and further, there is no evidence that the meningococci in meningococcæmia are "rough," and therefore less virulent strains. Only in one case (Marlow, 1929) was it noted that the organism had the characters of what we now call "roughness." We have not at present any method, apart from crude tests of its toxicity, and observations on its smoothness or roughness, of estimating the virulence of a meningo-coccus. Virulence is a relative term which can only be interpreted as the sum total of the evil effects produced in a particular species, and includes invasiveness in all senses of the word, toxicity, power of multiplication in the body and avidity for particular tissues, along with the power of combating the humoral and cellular defences of the host. It becomes even more complicated when it is realised that mechanisms of defence such as phagocytosis by polymorphs may assist in the dissemination of living meningococci by the blood stream throughout the body (Shearer and Crowe, 1917). Defence mechanisms sometimes go wrong.

The Persisting Focus of Infection in Meningococcæmia

The *nasopharynx* is the most obvious possible site of persisting infection by the meningococcus. In the series of 262 cases there were, as already stated, 47 in which throat swabs were examined for meningococci, 4 of which were routine examinations prior to discharge. In the 43 patients on whom tests were made, sometimes more than once, 33 gave negative results. In 5 of these repeated examinations were made.

The meningococcus was thus obtained from the throat in only 10 cases. The best authenticated case in which there was persistence of the organism in the throat for over two months is Stewart-Wallace's (1936) first case in which Type 1 meningococcus was obtained from the nasopharynx after two months and three weeks of illness. Type 2 meningococcus was obtained from the throat of Lambie's (1938) case

after three weeks' illness. Friedemann and Deicher (1926) wrote of their second case that pure cultures of "meningococci" could be obtained repeatedly from the throat during the 24th to 37th days of illness, but details of the identification of the organism, biochemically and serologically, were not given, and there was the same lack of complete identification, necessary in throat cultures, in the case of Krusen and Elkins (1937), in which cultures yielded "meningococci" up to the end of her three months' illness, with recovery. In the case of Price and Singer (1931) a nasopharyngeal swab taken on the fifteenth day of illness yielded no meningococci, but another taken on the seventy-sixth day yielded an atypical meningococcus differing serologically from that previously obtained by blood culture. In the other positive cases either the organism was not serologically identified, or the period of the illness when it was recovered not stated.

It may be that in some cases there was a failure to obtain the organism when present. On the other hand, there is the fact that in five cases repeated examinations of the nasopharynx were negative. We have therefore less than 25 per cent. of the cases examined affording evidence that the nasopharynx was the persisting focus of infection in meningococcæmia, while in 75 per cent. there was definite evidence that it was not.

It would have been reasonable to suppose that cases of meningococcæmia might be a special class of nasopharyngeal carrier, differing from the ordinary carrier in that either the organism is rather more virulent or the barrier of defence rather less complete ; thus being a half-way stage between the healthy carrier and the case of meningitis. But the facts are as stated. It is, however, possible that the organisms are below the surface of the nasopharynx or tonsils and inaccessible to ordinary swabbing.

It is natural that the *accessory sinuses* should be suggested as the focus of infection in meningococcæmia. Cleminson (1918) thought that the evidence pointed in the direction of the accessory sinuses being the main seat of meningococcus infection in carriers, and Embleton (1936) in a letter to the editor referring to Stewart-Wallace's (1936) cases of meningococcæmia suggested that the primary reservoir from which the blood stream was invaded might have been a sphenoid sinus empyema. Other authors such as Friedemann and Deicher (1926)— who tend to treat other assumptions also as facts—and Roger and Poursines (1932) write as though it were a generally accepted fact that the focus of infection in meningococcæmia is in the accessory sinuses, although the latter failed to find it in their case.

In the 262 cases of meningococcæmia under review, proof of sinus infection was to be found in only 3, as detailed in the second paper : in 1 per cent. In 4 cases X-ray examination showed no abnormality of the sinuses, and in other 3 there were negative bacteriological examinations. It is evident that only a small percentage had symptoms suggestive of sinus infection.

There is no other evidence as to the focus or foci in which meningococci persist during these long illnesses of weeks, months and even years. It is known that the reticulo-endothelial system in the course of its scavenging work may harbour organisms for long periods, and if this is the case in meningococcæmia the organisms would persist in these cells in organs and tissues such as the liver, spleen, lymph glands, adrenals, pituitary and bone marrow. Lymphatic glands are rarely enlarged or tender in meningococcæmia, but the spleen is palpable in 8 per cent. of cases, and there is sometimes pain in bones. If meningococci persist in reticulo-endothelial cells we must accept that they are capable of continued existence in the very cells which are the site of production of antibodies. It is believed that protozoa in these cells are protected from the action of chemical drugs. It would seem that meningococci could only persist in these phagocytic cells if substances such as complement, opsonins and bacteriotropins were cut off from them.

Salomon (1902), describing the first case, speculated as to the focus and suggested the *skin, or tonsils and air-passages*. The nature of the skin lesions is compatible with one of the early theories of persisting foci of infection; that in plugged capillaries organisms may be cut off from circulating antibodies. But this does not explain those cases in which there are no skin lesions. Ribierre, Hébert and Bloch (1919) suggested that the organism might persist in *foci of lymphatic tissue surrounding vascular and nervous tissue* near the meninges, external to the ependyma, or in the choroid plexus. It has been suggested by others that endocarditis is much more common in meningococcæmia than is supposed, and that the *endocardium* is the persisting focus, but there is no evidence that this is so. It is possible that the organisms persist in the *phagocytic cells in the blood stream*, or in the *endothelium lining blood vessels* and that the blood is never actually free of infection, but the intermittency of the condition is against this.

THE CAUSE OF INTERMITTENCY IN MENINGOCOCCÆMIA

Causes which suggest themselves are (1) that the organism goes through a life cycle, (2) that there is a rhythm in the relation between bacterial multiplication and antibody production, or (3) that the organisms being in a focus shut off from antibodies require a certain time to multiply so as to invade the blood stream in sufficient force.

There is (1) no evidence that meningococci go through a life cycle. As regards (2) such evidence as is available suggests that there is a rising titre of antibodies during the first two or three weeks of meningococcal infection, after which they remain stationary in amount for a time. There is no evidence of periods when antibodies fall and permit the overgrowth of the organisms, though it must be admitted that recorded observations are scanty. The most probable explanation is (3). Presumably, after a period of multiplication, the cocci invade

the blood stream by lymph channels, and continue multiplying till the defensive mechanisms, chiefly phagocytosis and lysis, destroy the cocci, and antitoxins neutralise the liberated toxins. It is reasonable to suppose that the chill or rigor corresponds with the period when phagocytes and lysins have destroyed the organisms and liberated endotoxin, and that the pyrexial period is due to toxæmia rather than bacteræmia. If this is so the optimum time for blood culture, when meningococci are most numerous in the blood, would be just before the rigor and not during the pyrexial period. If, on the other hand, the chill corresponds to the process of multiplication in resisting foci, or the emergence of cocci from these foci, the optimum time for blood culture would be during the pyrexial period.

IMMUNITY REACTIONS IN MENINGOCOCCÆMIA AND MENINGITIS

The toxin produced by the meningococcus is an endotoxin. Exotoxin, if produced at all, is small in amount. Antibacterial action is therefore important in the mechanism of defence. The demonstration of the development of antitoxin is difficult, as it is not certain that endotoxin has ever been obtained free from bacterial substance, and it is much less specific and antigenic than exotoxin The most important mechanism of defence is probably that of phagocytosis and bacteriolysis, with, presumably also, neutralisation of the liberated endotoxin by anti-endotoxin. A good serum should also · possess tropins to prepare the organisms for phagocytosis, and bodies to stimulate the phagocytes.

In the series of 262 cases of meningococcæmia reviewed, there were 48 in which the agglutinating power of the patient's serum was tested *versus* the infecting organism. It varied from no agglutination with undiluted serum up to an end titre of 1 in 300. In one of Bittorf's (1915) cases there was agglutination at an early stage to 1 in 5000, and later to 1 in 400. Omitting this case, in which the duration of meningococcæmia before the onset of meningitis was less than a week and in which the figure of 1 in 5000 must be considered dubious, we have 1 in 300 as the highest recorded dilution of the patient's serum agglutinating the infecting organism.

This is similar to the results obtained in cerebrospinal meningitis. Van Rooyen and Morris (1941), for example, found that the agglutinating power of the patient's serum against his own organism varied in a series of cases from nothing to 1 in 240. It was highest as a rule about the twenty-first day of illness, when it frequently reacted in a dilution of 1 in 120 to 1 in 240. It may be mentioned also that demonstrable antibodies in meningococcus carriers are of low grade.

The titres of the few cases in the present series tested against stock strains of meningococci was of the same rather low order. Of 5 cases tested, 2 showed no agglutination of meningococci, and 3 agglutinated the organisms to titres of from 1 in 25 to 1 in 400.

Complement fixation tests, with meningococci as antigen, were

negative in one case, and slightly positive in 2, but in Denmark this test is regarded as of value in diagnosis, both in cerebrospinal meningitis and in meningococcæmia, and Thomsen (1925) reported that the blood of 11 out of his 12 meningococcæmic cases gave a strong positive reaction ; the antigen was the Danish type A meningococcus.

The gonococcal complement fixation test, that is with gonococcus as antigen, was positive in 1 case, negative in 3 others.

Bactericidal tests with the patient's serum have been used in meningococcal infections, and Silverthorne and Cameron (1941) found a rising titre in meningococcæmia. No comparative estimations of phagocytic activity, or of antitoxic power were carried out in the cases reviewed.

There is therefore no evidence from these figures that there are greater amounts of protective substances in meningococcæmia than in meningitis.

From the point of view of *diagnosis* the agglutination reaction is too inconstant and often too weak to be of much practical value. The Danish workers write favourably of the meningococcal complement fixation test, and it is evidently of some value in epidemics. The difficulty in sporadic cases is the lack of clear differentiation between meningococcal and gonococcal infections owing to these organisms having antigens in common.

The *protective* action of phagocytosis and lysis is only the first stage in a defensive process ; it may, if it stops there, have an adverse effect. As Murray (1929) has pointed out, the massive liberation of endotoxin which results from phagocytosis and lysis in inoculated mice may lead to death of the host ; while in man a therapeutic serum which stimulates this defensive reaction may similarly lead to a deterioration in the patient's condition if it is deficient in anti-endotoxin. This is borne out to some extent by the occasional bad effect of serum therapy in cases of meningococcæmia. In Stevenson's (1931) case, for example, it was thought that serum had been harmful : ecchymoses occurred after its use, due probably to the liberation of toxins. This patient was shown, post-mortem, to have enormous numbers of meningococci throughout the tissues. Some workers believe that endotoxin is not antigenic and that therefore there can be no such thing as an anti-endotoxin. But whether endotoxin exists free in the body or whether it is really particles of protein from disintegrated meningococci, it does seem that a good serum has the power of neutralising it. It is a very weak toxin, as shown by the comparatively good condition of many cases of meningococcæmia. In fulminating meningococcal septicæmia it must be present in enormous amount, and the immediate improvement sometimes following the use of sulphonamides in these massive infections is very difficult to understand.

Most of the antimeningococcal sera have been prepared by the injection of whole cocci. Gordon attempted to prepare a pure anti-endotoxin serum, but it seems doubtful if he ever obtained pure

endotoxin. Ferry claimed to have produced exotoxin and to have prepared anti-exotoxic sera. Recent improvements in the preparation of antimeningococcal sera have been in the use of virulent capsulated meningococci in their phase of most specific antigenicity, and in the purification and concentration of the sera, with removal of the albumen, and retention of the globulin fraction.

Meningitis and Intermittent Bacteræmia due to other Neisseria

Meningitis, with presumably a primary bacteræmia, is sometimes caused by other Neisseria. *Diplococcus crassus* has been met with from time to time (Railliet, Téchoueyres, Ginsbourg and Pillement, 1929), once at least in epidemic form. Branham (1940) recorded cases in the Chicago epidemic of meningitis the organism from which gave a yellow growth and was not agglutinable by group sera ; it was styled *Neisseria flavescens*. This organism has been found in meningitis in France also (Emile-Weil, Duchon and Bousser, 1933). Similar infections by *N. catarrhalis* have been reported by Zoeller, Andrieu, Crosnier and Passa (1933), and others, but. the identification of the organism in some of the cases is suspect.

Cases of *intermittent pyrexia*, clinically resembling meningococcæmia, have been reported as due to *N. catarrhalis*. In Nagell's (1928) case the organism was not completely identified, and in Smyth and Cameron's (1930) three cases in soldiers it may well have been a meningococcus. Hugonot and Friess (1933) reported a case in which they believed the circulation was invaded by this organism from a pulmonary abscess. Bloch and Hébert (1920) reported a case which clinically resembled meningococcæmia but in which the organism was finally proved to be a gonococcus. Such cases appear to be rare.

Blood Culture in Meningococcæmia

The majority of the cases were diagnosed by blood culture, and it had been hoped that an analysis of the abundant material might provide the answer to some important questions. The results are on the whole disappointing. There is a lack of detail in some respects, and there were no large scale comparative tests of different methods.

As regards *culture media* used, fluid media, simple or enriched, were usually used in Britain and France, and solid media, plated out after incorporation of the blood, by many of the German and American workers. Many workers thought that it was necessary to use media enriched by serum or ascitic fluid, but others had results apparently as good with simple media, and it is a little difficult to understand why it should be necessary to add such substances to a medium already enriched by the patient's blood. Glucose broth was used by Dickson, McKinnon, Magner and McGillivray (1941) in an extensive series. Special media such as brain broth, and incubation in a CO_2

jar were used by other workers with varying results. Fluid media probably yield a larger number of positive results than solid media, but the latter have the advantage of permitting an estimation by colony count of the number of cocci per cubic centimetre of blood, and there is a greater possibility of isolating the organism if the primary culture has been contaminated. There was a remarkable lack of reference to contamination by most of the writers, from which it may be concluded that at least some of the negative results were due to contamination.

The time taken before *development of the culture* was very variable, the average being about 3 or 4 days. Occasionally development took place in one day, but as a rule growth was slow, and in one of Heinle's (1939) cases three blood cultures were positive only after fourteen days' incubation. It was observed that a culture might develop in one day, while another, taken from the same patient under apparently identical conditions, might take several days to develop. It was also noted by Hyland (1929) that a culture in fluid medium may remain clear and apparently sterile when viable meningococci are present within the white cells of the blood at the bottom of the vessel. It is thus necessary to make repeated subcultures even if there is no visible growth in the fluid medium.

There was no special *stage of the illness* particularly favourable for blood culture. Appelbaum (1937) found that in the majority of cases positive results were not obtained from cultures made before the third week of illness, and other observers have written to the same effect. There does not seem to be much in this. Positive results have been obtained on the fourth, sixth and eighth day of illness, and several times in the second week. In many, the first blood culture was not made till the third week or later, and it is evident that sometimes cultures were discarded too quickly before it was realised that the case might be meningococcal.

As regards the optimum time for culture in relation to *rigors, pyrexial period and skin efflorescence*, there is surprisingly little exact information to be derived. Most of the cultures were taken during a pyrexial period, and it was evidently the common belief that this was the optimum period; many positive and many negative cultures were obtained. A few took their cultures during rigors. Dock (1924) for example had two negative and two positive cultures during chills, and Veillon, Martin and Roux (1929) had a positive culture taken during a chill. In most cases there was no exact information as to the stage in the pyrexial period at which cultures were made. Kilham (1942) had two positive cultures taken just before the peak of the temperature, and two negative taken when the temperature was falling, but a much larger number of such observations would be necessary before any conclusion could be drawn. It is unfortunate that details as to the times of taking blood were not given for the repeated cultures of Dickson, McKinnon, Magner and McGillivray (1941).

Cultures were not usually taken in apyrexial periods, but there were occasional positive results at these times, as in the first case described in the first part of the present communication. As regards skin efflorescence, most of the positive cultures were taken when crops of skin lesions were present, these coinciding with pyrexial periods, but some cases with no skin lesions had positive cultures, and others had negative cultures when skin lesions were active. The atypical case of Martin and Dansie (1944) for example, with daily crops of skin nodules and only occasional pyrexia, had negative cultures save during one of the rare pyrexial periods.

The *number of organisms per cubic centimetre* of blood as judged by the colony count in solid media has been claimed to be of value in prognosis. There is not actual evidence from the figures that this is the case. The number varied from one or two per cubic centimetre to 75 or so, but in Adler's (1922) case which showed this last figure in one culture, there were still 30 cocci per c.c. in the last pyrexial period before convalescence ; an unfavourable prognosis based on the large number of organisms still in the blood would have been quite wrong. It has been suggested also that an increase in the number of organisms per cubic centimetre is one of the signs suggestive of the onset of endocarditis. This may be so, but exact figures have not been given. It is probably true that higher counts may be obtained when there is endocarditis. In Willius and Eaton's (1937) case, for example, there were colony counts up to 100 per c.c., and Zeissler and Riedel's (1917) first case showed counts up to 150 per c.c.

All writers are agreed as to *the inconstancy* of results, and that *repeated cultures* may be necessary before a positive result is obtained. In the series of Dickson, McKinnon, Magner and McGillivray (1941), for example, 10 blood cultures were made in one case of which 4 were positive, 21 in another of which 2 were positive, in a third 14 with 12 positive, and in a fourth 6 with 4 positive.

A difficulty is in determining the most suitable proportions of blood and medium ; if too little blood is added the chance of successful cultivation of scanty organisms is diminished ; if too much, anti-bacterial substances may have an inhibitory effect.

BACTERIOLOGICAL EXAMINATION OF SKIN LESIONS

The microscopic nature of the hæmorrhagic skin lesions in meningo-coccal meningitis and fulminating meningococcal septicæmia was studied during the 1914-1918 war by Benda (1916), Babes (1916), Netter and Salanier (1916), Pick (1916), Netter, Salanier and Wolfrom (1916), and independently, owing to war conditions, by Muir (1919). They all demonstrated the inflammatory nature of the lesions and the presence of meningococci in them. It had previously been thought that the changes were toxic in origin, but Muir in particular demonstrated that the cocci might occur in large masses leading to the

blocking of the minute vessels and thus to hæmorrhage, though he considered that toxins might play a part.

Renault and Cain (1920) found that the sweat glands were infected by meningococci, as well as the capillaries and arterioles. Brown (1924) found the most marked lesions in the subcutaneous tissue, in which the vessels were engorged with leucocytes, many containing meningococci; there was hæmorrhage in the adjacent fat tissue. Bourdellès (1925) studying 26 cases of " infective purpura " suggested that the finding of meningococci in petechiæ was sometimes the best method of diagnosis. McLean and Caffey (1931) demonstrated meningococci in smears from purpuric exanthem in 15 out of 18 cases of acute fulminating infection in young children.

These, however, were all cases of acute septicæmia, and a classing of acute and chronic septicæmic cases in one category led to conclusions derived from these observations being applied unjustifiably to the chronic type of infection. Thomsen and Wulff (Thomsen, 1925) described a technique which they claimed was successful for the demonstration of meningococci in the skin in nearly 100 per cent. of cases. Thomsen did not differentiate clearly between acute and chronic cases of meningococcal septicæmia, and it seems that the epidemic at which he and Wulff were working in Denmark between 1917 and 1920 included an unusual number of acute septicæmic cases. Their method involved the excision of a piece of tissue during life or as soon as possible after death, and making cultures and sections from the subcutaneous tissue. But other workers have had comparatively little success in skin examinations in cases of definitely chronic meningococcal septicæmia. Köhlisch (1915) said that attempts to grow the meningococcus from skin lesions failed. Friedemann and Deicher (1926) found a few cocci in capillaries in slides made from a skin lesion, but they could not be differentiated. Kennedy (1926) obtained a growth of Gram-negative diplococci from an excised papule. Master (1931) found Gram-negative diplococci, intra- and extracellular, in a biopsy of a skin lesion. Harrison and Abernethy (1934) found no organisms in a biopsy of a papular lesion, but in another case they once obtained a growth of a Gram-negative diplococcus contaminated by a staphylococcus; other cultures were negative. Richter (1934) found numerous pus cells in smears of petechiæ, but no organisms; cultures on enriched media remained sterile. Appelbaum (1937) made several biopsies on the skin lesions of a case but all were negative for meningococci. So far, therefore, bacteriological examinations of skin lesions in meningococcæmia have not proved of much diagnostic value. Even in the cases in which skin lesions became pustular, it seems to have been very rare to cultivate meningococci. It is probable that negative results were sometimes due to failure to recognise that the organisms were most numerous in the subcutaneous tissue, and that excision to a certain depth is necessary.

It is clear that in acute and fulminating infection there are large

numbers of meningococci in and beneath the skin, both free and within the numerous polymorphs, and that the capillaries are plugged with organisms and polymorphs, with resultant rupture and hæmorrhage. Toxins liberated from broken-down organisms no doubt play their part by their action on the endothelium of the capillaries. The petechiæ of the chronic meningococcæmia cases are probably produced in a similar way, though the number of organisms scattered in the skin during each pyrexial period is probably less. The mechanism of the production of the papules and nodules of the meningococcæmic cases is not so clear. The natural and probably correct assumption that these are due to bacterial emboli is not entirely supported by the results of bacteriological examinations, but as suggested above this may partly have been due to defective technique. It seems also that there is a greater tendency towards escape of plasma, with consequent local œdema, than towards hæmorrhages. The œdema is in the deeper layers of the skin and in the subcutaneous tissue, hence the firm nature of the swellings. Probably sensitisation of the skin by the intermittent bacterial attacks is partly responsible for the nature of the lesion.

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THE TREATMENT OF CHOLERA BY INTRAVENOUS SALINE INJECTIONS; WITH PARTICULAR REFERENCE TO THE CONTRIBUTIONS OF DR THOMAS AITCHISON· LATTA' OF LEITH (1832).

By E. D. W. GREIG, C.I.E., Lt.-Col. I.M.S.(Ret.)

THE pandemic of cholera, which started from Bengal about 1823, introduced Asiatic cholera to Europe for the first time. It reached Edinburgh early in 1832 from Newcastle, which was attacked towards the end of 1831. From Newcastle it did not spread directly to Edinburgh, but halted for a time at Haddington.[1] The slow rate of spread of the pandemic from Bengal was regulated by the speed of transport, which was chiefly by foot in these days. With increased speed of transport by railways, etc., subsequent pandemics of cholera reached Europe much more quickly.

In Edinburgh and district the epidemic lasted nearly nine months, displaying such a degree of virulence as to destroy in a very short space of time the majority of those attacked.[2] The epidemic could be divided into three phases : (*a*) From February to 14th June; (*b*) 15th June to 31st July ; (*c*) 1st August to 1st December. The total number of persons attacked was 1885, and of these, 1065 succumbed. More females than males were attacked.

That the great majority of the medical profession in Great Britain in 1832 were quite unprepared for the treatment of cholera is indicated by the fact that about twenty-four different methods of treatment were advocated. These included, the actual cautery ; bastionading the feet ; suffocating under a feather bed ! The list was humiliating to the profession, but there was at the time much excitement and anxiety amongst medical men, so much so that many lost their reason.[3]

Fortunately, during the epidemic, a very important contribution to the problem of the therapy of cholera, based on sound scientific principles, was made by Dr T. A. Latta of Leith, who is now recognised [4] as the pioneer in the treatment of cholera by intravenous saline injections. That it was courageous therapy at that distant· period there can be no doubt, because even at the present time (1944) the Medical Society of London have discussed the difficulties and dangers of intravenous therapy.[5] In addition to the difficulties and dangers of the treatment he also encountered discouraging obstruction from some of his colleagues in carrying .it out.

It is remarkable that, so far as can be ascertained, no obituary notices of Latta or of the two colleagues who co-operated with him appeared in any medical journal. To fill the gap the following biographical facts are given regarding Latta and his two colleagues, Mackintosh and Lewins :—

Thomas Aitchison Latta graduated M.D. (Edin.) in 1819 with a thesis, *De Scorbuto*. He resided at 32 Bridge Street in 1822; 1 Sandport Street, 1825; 27 Constitution Street, 1827; 15 Charlotte Street, all in Leith (now incorporated in the City of Edinburgh). He died at the latter residence on 19th October 1833, of consumption "occasioned by his unwearied and unremitting exertions on this occasion (cholera epidemic)." [3] His contributions are dealt with fully later.

John Mackintosh graduated M.D. at Aberdeen University in 1820. After serving in the Ordnance Medical Department he settled in Edinburgh and practised at 31 Albany Street. He lectured in the extramural school on the Practice of Physic and was the author of a book in two volumes on this subject. He was in charge of the cholera hospital at Drummond Street in 1832. He died at Edinburgh on 28th October 1837.

Robert Lewins graduated at Edinburgh in 1813 and became a Fellow of the Royal College of Physicians of Edinburgh on 2nd November 1830. He practised in Leith, where he resided at 6 Quality Street.

Latta adopted the intravenous saline method for the treatment of cholera after reading a report on the analysis of the blood in cholera by O'Shaughnessy. [6] The latter showed that the blood in cholera had lost a large proportion of its water, 1000 parts of cholera blood serum having lost on an average 860 parts of water; it had also lost a great proportion of its neutral saline ingredients; he also noted that all salts deficient in the blood, especially carbonate of soda, were present in large quantity in the peculiar dejecta. Latta [7] had the ability to grasp the implication of these findings and applied the knowledge in his treatment of cholera. He sought to restore the blood of cholera cases to its natural state. At first he tried injecting large quantities of warm water, containing the requisite salts, into the large intestine, and also giving it by mouth. Finding this method and all others to be useless, he resolved to throw the solution direct into the circulation. This he proceeded to do with much caution. He described the solution employed for intravenous injection as artificial serum. It was prepared by saturating water with protoxide of nitrogen holding in solution half a drachm of muriate and eight grains of subcarbonate of soda to the pound (pint) of water. He gives the following account of the first cases treated by him :—

CASE 1. Male, aged 33. In complete collapse stage of cholera. He was given 60 oz. of saline solution intravenously at a temperature of 98° F. Every symptom was permanently removed. No consecutive fever. He was convalescent in four days.

CASE 2. Male, aged 48. Severe case of cholera, seemed hopeless. He had chronic liver and gastric disease. Given seven pints of solution intravenously. This had only a temporary effect. Then given six pints at temperature of 96° F. Next day pulse failed, injection repeated. Fifty hours after first injection he passed urine. Every symptom removed. No consecutive fever.

CASE 3.   Female, aged 65.   Very advanced case of cholera.   Intravenous saline prolonged life, but she died next day.

CASE 4.   Male, aged (?).   In an advanced stage of cholera.   Two pints of saline intravenously at 98° F. only required.   There was immediate relief, stools became feculent next morning and he passed urine.

CASE 5.   Female, aged 45.   Advanced stage of cholera.   Two pints of saline intravenously at 97° F.   Vomiting and purging stopped.   Again given two pints of saline.   Stools feculent and she passed urine.   She did well.

Latta attached great importance to the use of a vapour-bath to maintain the body temperature as an adjuvant to the intravenous therapy.   As we will see, Wall found hot water baths of considerable value as a supplement to intravenous therapy in the treatment of cholera.

The Lancet, in a leader [8] on Latta's work, says : " . . . a paper of considerable interest, written by Dr Latta of Leith, detailing several cases of malignant cholera, which, by the intervening agency of the vapour-bath, were successfully treated with saline venous injections at a period of the disease when, without the aid of the auxiliary Dr L. now proposes, the patients would almost certainly have perished. . . . The contrivance is a very good one."

In a further paper,[9] Latta amplifies his account of his method of treatment.   He recommends that the temperature of the fluid injected should be 112° F., because 100° F. is too low and produces an extreme sense of cold and rigors ;   at 115° F. it suddenly excited the heart, the countenance became flushed and great weakness was complained of.   He also recommends that the rate of injection should be very slow, not exceeding two to three ounces per minute.   The quantity of fluid required will depend on the effect produced, and the repetition of the injection on the demands of the system, which will vary according to the violence of the diarrhœa.   The greater the collapse the greater the quantity as a rule.   Failure of the treatment is due to (1) quantity of fluid being too small, (2) extensive organic disease, (3) application of treatment too late.   The evil of consecutive fever is mitigated by intravenous saline.   The apparatus employed by Latta was a Read's patent syringe with a small silver tube attached to the extremity of the flexible injecting tube.   The syringe should be in perfect condition to avoid injection of air, the vein should be treated with much delicacy to avoid phlebitis, and injection should never be made more than once at the same orifice.

. Lewins, Latta's colleague, in a letter [10] to The Lancet, dated 14th June 1832, says : " . . . The failures we have witnessed, in my opinion, afford no real objection to the practice of treating cholera by venous injection—a method of medical treatment which, as I said before, will, I predict, lead to important changes in the practice of medicine, and will entitle Dr Latta's name to be placed amongst the number of those (alas ! how few) who have really contributed to the improvement of the healing art."

A very dangerous method of applying Latta's treatment occurred

to Dr T. J. Murphy of Liverpool. He writes: [11] " Having read Dr Latta's paper, my first idea was to return into the system the alvide dejections by injecting them into the venous system ; an idea which arose from a quantity having been preserved for my inspection." Fortunately for the patients he was prevented from carrying out the idea by the dejections being seldom preserved. He then prepared an artificial serum as recommended by Latta.

Dr John Mackintosh was in charge of the special cholera hospital in Drummond Street, Edinburgh, during the 1832 epidemic. He gave the intravenous saline treatment an extensive and accurate trial, treating 156 patients by this method. He writes: [3] " The bold idea of restoring the loss at once, by injecting a large quantity of saline solution into the venous system, occurred to the original mind of the late Dr Latta of Leith. . . . He was ably and zealously supported in his investigations by Dr Lewins, who encouraged and assisted him, when others threw every obstacle in the way of his experiments, and too often gave erroneous reports of his practice." Mackintosh used the following solution :—

Sodium chloride .	.	.	.	.	half an ounce
Sodium bicarbonate	.	.	.	.	thirty grains
Water	.	.	.	.	.	Ten pounds (pints)

This solution was in use from 12th May to 21st August 1832, when the quantity of each salt was doubled. The temperature of the fluid was from 106° to 120° F. The solution was strained through chamois leather. Great care in the preparation was recommended. Two persons were employed in the operation, one to open the vein, introduce the tube and keep it in position ; the other to take charge of the apparatus and fluid injected. An assistant to be at hand to do anything required, so that the attention of the operators may not be distracted. Care was taken to avoid the introduction of air, and fluid was pumped through the tubes for a few moments. Ten pounds (pints) were introduced in thirty minutes. Mackintosh noted the following effects of the injection : (1) *Pulse*. It was speedily made perceptible after four ounces, good after three pounds (pints). The quantity of fluid injected depended on the state of the pulse. (2) *Cramps*. The effect was quite remarkable, they ceased as soon as pulse improved and seldom recurred. (3) *Temperature*. The effect was almost instantaneous, the body became warm with a gentle and genial perspiration. (4) *Respiration*. This became stronger ; sometimes after four pounds it became laboured, but improved with more fluid. (5) *Countenance*. Eyes became prominent, expression animated and mind lively. (6) *Restlessness and uneasy feeling*. This vanished. (7) *Thirst*. This ceased, however urgent. (8) *Secretion of urine*. Soon returned, but in this he was more frequently disappointed than in any other favourable symptom. (9) *Period of death*. This was undoubtedly postponed. (10) *Rigors*. These were almost invariable after the injections. He treated in all one hundred and fifty-six

cases of cholera by intravenous saline and twenty-five recovered. He considered that not one of the cases treated had a chance of recovery by any other means and adds : " We saw no such miracle out of 461 cases (291 deaths) in Drummond Street hospital." He concludes : " Should I ever have charge of cholera patients again, I shall, profiting by the experience I now possess, use the saline solution at an earlier period of the stage of collapse, nay, at its commencement, in order to lessen the thickness of the blood before organic mischief is done. In looking over the cases, my only surprise now is, that one of the individuals recovered by any means that human ingenuity could suggest." He tried the addition of albumin (white of egg) to the fluid to make it resemble the serum of the blood as closely as possible, but he did not find that there was any beneficial effect, so it was laid aside.

In the same year, 1832, as the pioneer work in Leith and Edinburgh was done, a trial was given to the method in the Madras Presidency, particularly by Surgeon John Grant Malcolmson,[12] M.D. (Edin.). He was assistant-surgeon in Madras in 1823, and surgeon in 1832. He treated cases amongst the Madras European Regiment at Secunderabad in 1832. The solution was carbonate and muriate of soda largely diluted in water, and injected into the venous system by means of the ordinary apparatus for blood transfusion. The quantity injected was at first one to two pounds at 98·6° F., subsequently increased to six to eight pounds in some cases. Improvement followed. However, the difficulties of the operation discouraged an extensive trial and apparently it was dropped. J. Macgregor, assistant-surgeon, 39th Foot, in a report [12] on cholera in Bellary, S. India, in April to May 1839, refers to Mackintosh's work on intravenous saline treatment, and says : " I would certainly resort to it in bad cases."

The following incident which occurred at the time, indicated that Latta had not only to contend with the technical difficulties of the treatment, but also with opposition from some of his colleagues. A leader in *The Lancet* of 4th August 1832 [13] records that " Dr T. Craigie of Leith wrote a letter published in the *Edinburgh Courant* on 14th June 1832, in which he did not make ' honorable mention ' of Dr Latta as the first physician who tried venous injections in cholera, which Dr Latta and his friends considered due from one writing at that particular time and under the existing circumstances. The omission was noticed in an anonymous letter in the *Edinburgh Observer.* This letter contained a remark which Dr Craigie, in a subsequent epistle, spoke of as ' false and unfounded.' The writer of the anonymous letter proved to be Mr John Mitchell, jun., Ship-broker of Leith, who confessed to the authorship for the purpose of demanding an explanation from Dr Craigie as to the above offensive words. An interview took place, casually, in the street, when a trifling assault, with a child's whip, was believed by Dr Craigie to have been committed on him by Mr Mitchell, who is an intimate friend of Dr Latta. The

parties were bound over to keep the peace, although (most unaccount-ably to the reader) Mr Mitchell denies (' does not admit ') that any assault took place, declaring, ' that he had not any whip in his hand when asked for the apology.' " As in the ' index ' on the cover of *The Lancet* of 4th August the heading read, " Quarrel between Drs Latta and Craigie," Dr Latta wrote to *The Lancet* [14] as follows : " The *quarrel* is not mine, but Dr Craigie and Mr Mitchell's, and originated not from any complaint on my part, but in consequence of Dr Craigie applying to a remark made by Mr Mitchell, the offensive term ' utterly false.' As for my name being coupled with venous injections, that is an honour I have not been remarkably fastidious about. The matter is too insignificant for you to revert to, or you would find I did not write to complain of the want of courtesy on this point, but was compelled to come forward in vindication of Mr Mitchell's integrity (who, unknown to me, made the remarks in the *Observer*), and in defence of my own conduct and practice, both of which have been misrepresented in Dr C.'s pamphlet." Dr Mackintosh also refers to Latta's difficulties with his colleagues. He writes : [3] " Few medical men can bear to know that the soundness of their opinions have been questioned : they regard any such attempt as a signal for deadly personal hatred, and view it in the same light as if their moral characters were maliciously assailed."

From the foregoing records it will be apparent that the *odium medicum* was very pronounced, and prevented certain of the profession from recognising a noteworthy addition to therapy.

The next contribution to the treatment of cholera by intravenous saline was made by E. A. Parkes [15] in 1847. He refers to Mackintosh's work. Like Mackintosh he tried the addition of egg albumin to the saline solution. Temperature of solution 98° F. He treated five cases with four deaths, and considered the revivifying effects of the albumin solution seemed to be as well marked as any recorded by the saline solution.

Forty-six years later, in 1893, valuable work on intravenous saline therapy was carried out by A. J. Wall [16] in India. He refers to the work of Latta and Mackintosh. His solution was :

Sod. chloride	four grammes
Sodium carbonate	two grammes
Water	one liter

The temperature of injection was 37° C. Injection made very slowly, not exceeding a liter in twelve minutes. The results of his first series of severe cholera were : out of fifty-eight cases treated, forty-one died, 70 per cent. mortality. In the second series one hundred and thirty-five cases were treated, and ninety-five died, 70 per cent. mortality. He recommended intravenous saline for other conditions in which de-hydration was a marked feature. It is also interesting to note that he suggested the addition of gelatine to give more permanent effect to the

solution. He made the important recommendation that rectal temperature in cholera should be taken as a guide to the temperature of the fluid injected. Like Latta he strongly favoured the warm bath for maintaining the body temperature. The range of temperature of the bath being from 32° to 37° C. The bath to be wheeled to the bedside; the patient, who should not exert himself, is placed in it at full length for from ten to fifteen minutes. It can be repeated again and again. The results are most striking. An important contra-indication is a high rectal temperature, 103° F. For hyperthermia he recommends an enema at 80° F. or considerably below this. In less severe cases he advised subcutaneous instead of intravenous injection of saline. The solution for this purpose should contain no alkali or anything that can cause the least irritation.

The next advance in intravenous saline therapy was made by Sir Leonard Rogers [17] in Calcutta between 1906 and 1915. He worked out his well-known standard method of treatment for cholera, which is now generally employed. By a simple clinical method the specific gravity of the blood is estimated, and the necessity of an intravenous saline injection can be ascertained before the patient has entered the stage of collapse, and it also gives an indication of the quantity of fluid required. He employed hypertonic saline, using two solutions; the first containing sodium chloride one hundred and twenty grains, and calcium chloride four grains to one pint of water. The second contains sodium chloride ninety grains, sodium bicarbonate one hundred and sixty grains to one pint of water. If four pints are required, then one pint of the alkali solution is given, followed by three of the hypertonic saline. He showed the importance of taking the rectal temperature. To avoid consecutive hyperpyrexia the temperature of the solution should not be above 80° F., if the rectal temperature is found to be above 101° F. Temperature of fluid should not exceed 98° F., except when the rectal temperature is below normal, then the temperature of the solution may be two to three degrees above 98° F. By the use of his scheme of treatment a striking reduction in deaths from cholera in hospital cases was brought about.

Recently Wilkinson,[18] from his experience of cholera in Hongkong, has expressed a preference for normal, instead of hypertonic saline, for intravenous therapy, because hypertonic saline injections were not found successful there during the epidemic in 1931, judging by mortality; also, theoretically, the main effect of hypertonic saline intravenously is to induce a flow of fluid into the blood stream, and the only place in the body which could yield it would be the gut, and this would mean in cholera more toxin absorbed from the gut, and more violent subsequent reactions.

From the above summary it will be seen that intravenous injection of saline solution is considered an essential method of treatment of cholera at the present time, and that Latta, in 1832, had the great merit of being the first to employ it in cholera. His treatment was not

empirical, but based on sound scientific observations. As would be expected the early technique was primitive, but the method has undergone progressive evolution and improvement; however this does not detract in the slightest degree from his bold and original conception. Looking at the technique with the advantage of present-day knowledge is interesting. For example, we see that the temperature of the fluid injected was too high, and might easily produce dangerous hyperpyrexia. Further, the injections were commenced at a very advanced and almost hopeless stage of the disease; this was clearly recognised by both Latta and Mackintosh in their reflections on the results after the cessation of the epidemic, and they rightly concluded that a very considerable improvement in the mortality rate would have been effected if the injections had been started much earlier.

From what has been stated in this paper, the importance of the work of Latta and his colleagues, as the pioneers of intravenous saline treatment of cholera, will be realised, and it is hoped that the statement will give them the place they deserve in medical history, and keep their memory green.

> The wisdom that they taught us
> Is proven prophesy.

I take the opportunity of expressing my indebtedness to Mr T. H. Graham, O.B.E., Librarian, Royal College of Physicians, Edinburgh, for kind help in the preparation of this communication.

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OBITUARY

RALPH STOCKMAN
F.R.S.Ed., M.D., F.R.C.P.E., F.R.F.P., and S.G.

RALPH STOCKMAN died in Edinburgh on 27th February 1946. Born in 1861, the second son of W. T. Stockman, merchant in Leith, he was educated at the Royal High School and the University. After graduating M.B., C.M. in 1882, he extended his study in Vienna and Strasburg. In 1883 he served as resident physician to Sir Thomas Fraser, and during the next six years was assistant in the department of Materia Medica. Later he became lecturer on Materia Medica in the School of the Royal Colleges. He was early attracted to research and was one of the original team of investigators in the Research Laboratory of the Royal College of Physicians when it was opened in 1889 under Sims Woodhead. His wide knowledge of chemistry and his painstaking technique soon made a name for him in this field.

Clinical work also made a strong appeal to Stockman. He was physician to the New Town Dispensary and the Deaconess Hospital and he collaborated with his friend, Sir Robert Philip, in his work for the tuberculous. Later he was appointed assistant physician in the Royal Infirmary. His clinical teaching was particularly stimulating ; those who attended his clinics were trained to observe and to think for themselves.

Stockman's eminence as an investigator and his reputation as a teacher were duly recognised in 1897 when he was appointed to the chair of Materia Medica in Glasgow. At this time the Faculty of Medicine was comprised of elderly men, good teachers but, apart from Bower and MacEwen, not active in research. Gairdner was past his best and soon was in indifferent health. The Materia Medica Department was poorly equipped, but a retiring room was immediately fitted up as a laboratory and research was set on foot at once ; the beginning of a museum was made in a store-room. From the first, Stockman infused new life into the teaching, and with the arrival of Muir and Noël Paton, Glasgow became a centre of research.

The chair of Materia Medica was a part-time one without any clinical responsibility, but in a short time Stockman was fortunate in becoming a physician to the Western Infirmary and was thus able to show the application of his art in a practical manner. Against considerable opposition he limited the size of his clinical classes, and in this way he was able to attract the more active students. His wards were run on a team system, and as far as possible all investigations were carried out by the staff of the ward. Specialist help was only called in when difficulties arose which baffled the team. He made great use of his ward visits, and bedside instruction was the basis of his teaching. Clinical lectures he gave weekly, but often, instead of giving his prepared lecture, he would take a casual case referred to him for investigation. On one occasion a man with severe anæmia sent from the out-patient department was thus made the subject of an impromptu clinical lecture. Eventually Stockman made a diagnosis of anchylostomiasis and this was confirmed by a rectal smear. As a clinical teacher he was most successful, ever emphasising the root cause of disease, and that diagnosis should lead to therapy.

His lecturing style was clear and easy ; master of his subject, he could put things very simply Careful preparation enabled him to use a minimum of notes, and a somewhat dreary subject was made interesting with anecdote

RALPH STOCKMAN

and wit. No roll was called, and if the lectures did not attract the student he need not attend.

Stockman recognised the value of a museum which would illustrate therapy, and made full use of all his clinical material, collecting photographs, pictures, charts, tracings and casts. The expenses of the museum he insisted on paying out of his own pocket, steadily refusing to accept help from university funds for its upkeep. In the end it was a very fine collection admirably suited to its purpose.

Throughout his long tenure of the chair, Stockman systematically carried out research. As consultant practice occupied the afternoons, research had to be planned so as not to require long spells of continuous work. Pure pharmacology did not attract him so much as the slow action of drugs comparable to ordinary therapeutic use. In this way he investigated the action of nicotine, iodides, bromides, arsenic, phosphorus and certain heavy metals. The problem of the rheumatic diseases attracted him. An attempt to discover a better anti-rheumatic than salicylate only resulted in more firmly establishing the old remedy. His investigations on the rheumatic nodule, fibrositis, muscular rheumatism and the chronic joint conditions formed the basis of his book on *Rheumatism and Arthritis*.

After retiring from the Infirmary, he turned his attention to Indian diseases and remedies and work on Khat and Lathyrism.

The papers in which he described his findings might well serve as models for medical writers. They are all short, the historical aspect being briefly presented, his own observations being lucidly described with a minimum of detail.

His occasional writings, often addresses to non-medical societies, are not so well known, but are of great interest from the historical data they contain.

His teaching and research work took only part of the time; for the rest of the day he was the busy consultant. In this he was very successful and in great demand. He was a " useful " consultant, a shrewd diagnostician and fertile in therapy. His verdict might sometimes give offence so that the patient would leave in a temper, but, as he said, they mostly came back as they found that he could do more for them than others could.

In University life he preferred to keep in the background, but he exercised great influence. He was a master in the use of the " tempo." He knew just when and how to use his influence.

His long connection with the Union kept him in touch with students of all faculties and lasting friendships were formed.

Material for the above has kindly been supplied by his friends, Lt.-Col. E. D. W. Greig and Professor F. J. Charteris. The following contribution is by Sir Robert Muir.

To what has been written with regard to the career and work of the late Professor Stockman I gladly add something, more especially from the personal point of view. I enjoyed his close friendship for more than fifty years, and thus came to know and appreciate his character and qualities as few had the opportunity of doing. His personality was a many-sided one, and some of his qualities were not readily understood; it was in the main characterised by individuality and by independence of judgment on the one hand and a peculiar kindliness and sensitiveness on the other. Independence was inherent in him and was nurtured by self-education. He read widely and thought deeply on any subject with which he was concerned; only then did he form

his opinion. Once it was formed, however, he held it with tenacity and never hesitated to express what he thought, and the fact that his views might be considered unorthodox did not prevent his expressing them; he preferred outspokenness to reticence for policy's sake.

Individuality is seen both in his original work and in his teaching. When he returned to Edinburgh as a young man after study and research with Schmiedeberg in Strasburg, he was accomplished in pharmacological investigation as were few men of his time, and it might have been expected that he would make this his life's work. Experimental research was continued throughout his life, the last important investigation being that on lathyrism, but at an early period he came to recognise its limitations in therapeutic advance, and clinical work became more and more the subject of his thoughts. On his appointment as physician to the Western Infirmary he gave his full energies to his hospital work. As a result of his clinical investigations an outstanding contribution was his book on rheumatism and fibrositis. Characterised as it is by original observation, independence of judgment and shrewd criticism, it has contributed more than any other work towards the understanding and treatment of the conditions dealt with. I saw much of this research in progress, and became increasingly impressed by his intense concentration on the subject and his sustained endeavour to understand the pathological changes and to reach the possibility of effective treatment.

In teaching, too, both in the wards and in the lecture-room, he evolved his own methods. His object was rather a training in mental attitude than in the imparting of information. Critical and even scornful of what he considered unworthy, he had a strong belief in certain therapeutic agents, and he emphasised the importance of their mode of use. He used largely the Socratic method, and his students were subject to testing questioning. He had come at an early period to recognise that clinical medicine could not be taught to large classes, and on obtaining wards he strictly limited his clinic to a relatively small number. This procedure, at that time unusual, met with opposition in certain quarters, but he insisted on it and he gained his object. In all his teaching, his purpose was to qualify his students for their life work in every respect. Besides training them by his own methods for their professional duties, he aimed also at developing character and general outlook. In this latter aspect one naturally associates his services in connection with the Students' Union. As Honorary President for many years, he gave time and labour to its requirements and he always insisted on the importance of the Union as an educative influence in University life. Few teachers have done so much as he did for the welfare of students, and many of them will acknowledge the help and stimulus they received from him.

Stockman played his full part in the business of the Medical Faculty and the Senate. But he had no special leaning towards administrative work as such, and it is a matter for no regret that he had not to devote more time to it. That he had a considerable faculty for such work, however, was fully shown by his services as Chairman of the Senate during the illness of Principal Rait. He discharged the duties with dignity, and business was carried out with increased brevity without impaired efficiency. Waste of words and waste of time in any form were distasteful to him, and terseness in expression was a feature in all his speaking and writing.

Stockman was a great reader, in fact he may be said to have found in reading his chief enjoyment. He was versed in the history of medicine as few men are, and could have given a course of lectures on the subject with

little preparation. Reference to the pioneers was frequent in his teaching, and he sometimes took pleasure in demonstrating that what often passed as novelty was not a new thing at all. His knowledge of the materia medica was almost unique. It embraced the action of drugs in every aspect, the evolution of methods of treatment and the abundant lore of the subject. Of general literature also he had an extensive knowledge. Books of the past, whether of prose or poetry, appealed to him most, especially those which had achieved the rank of classics. Distinctly selective in his tastes, he had at the same time keen appreciation of standard in literature. He had a remarkably retentive memory, which fortunately remained with him till the end, and in talking with him one was often struck by the detailed knowledge which he brought out of his store of erudition. Music and the fine arts were of less interest to him, though he found pleasure in the best of them. His likings, however, were factual and speculative rather than artistic.

In outdoor pastimes and sports he had comparatively little interest. Up till some years ago he played golf, and I had many a pleasant round with him; but I think he enjoyed the pleasant surroundings and the exercise more than the game itself, and his thoughts were often elsewhere. His favourite exercise was walking, and up to the commencement of his last illness he indulged freely in it, sometimes doing twenty miles in a day. He drew intense enjoyment from the sights of nature and the countryside, and notably from places with historical association. And one must not omit to mention that in his later years his garden and his bee-keeping were a constant delight to him. He was thus a man of essentially simple tastes.

Stockman led a simple and at times a rigorous life and was scornful of the self-indulgent; but at times his customary seriousness was happily broken and he had full enjoyment in an occasional convivial meeting, often enlivening it by his fund of humour and his store of anecdote. His sense of humour was indeed one that was all his own. In all his dealings with his patients and his fellows he had a high ideal of service. Any good cause which appealed to him had not only his sympathy but received his unstinted support. His professional life was one of devotion, and no consideration other than his patients' welfare ever entered into it. His kindliness and sympathetic understanding endeared him to his patients, and he won their affection equally with their confidence. He had still another quality which was not so generally known, namely a tenderness of feeling, a sensitiveness to the sufferings and trials of others. To friends of his inner circle he was deeply attached, and the loss of any one of them cut him deeply; he seemed, too, to participate in the sorrowful experience of others. Generosity was another of his characteristics; he gave lavishly, sometimes even uncritically.

Throughout his last illness he showed the utmost fortitude and patience. It was a long and trying one attended by much discomfort, often with attacks of pain and breathlessness, and, what he regretted most, by an increasing interference with his powers of walking. Yet in talk he made little reference to his disabilities. He retained in a remarkable way his sense of humour and his interest in things in general; his smile would readily break out as of yore. During these last years I paid him many visits, each of which threw fresh light on the remarkable width of his knowledge and the diversity of his interests. My intercourse with him was a source of sincere pleasure to me, and I count it a great privilege to have had it. A great and interesting figure in medicine has gone from us, a man honoured and esteemed by all who knew him.

NOTES

A QUARTERLY Meeting of the College was held on 7th inst., the President,
Dr D. M. Lyon, in the Chair. Dr T. Carlyle Mitchell
(Radlett, Herts) and Dr Oscar Olbrich (Edinburgh) were
introduced and took their seats as Fellows of the College.
Drs A. H. Campbell (Redhill, Surrey), N. G. Pandalai
(Vizagapatam, India), N. F. Lilauwala (Bombay), Gordon O. Horne (Edinburgh) and Stanley G. Graham (Glasgow) were elected Fellows of the College.

Royal College of Physicians of Edinburgh

AT a meeting of the Royal College of Surgeons of Edinburgh, held on 16th
May, Mr James M. Graham, President, in the Chair, the
following who passed the requisite examinations were
admitted Fellows :—Herbert Michael Bradmore, M.B.,
CH.B. UNIV. EDIN. 1942 ; Aziz El-Masri, M.B., CH.B.
UNIV. CAIRO 1930 ; Alan Anderson Finlayson, M.B., CH.B. UNIV. ST ANDREWS
1937 ; Archibald Lamont Goodall, M.B., CH.B. UNIV. GLAS. 1937 ; M.D.
1944 ; Richard Swinton Hunt, M.R.C.S. ENG., L.R.C.P. LOND. 1935 ; Ranulph
Rex Hunter, M.B., B.CH. UNIV. CAMB. 1940 ; Wilfred Charles Lawrence,
M.R.C.S. ENG., L.R.C.P. LOND. 1939, M.B., B.S. UNIV. LOND. 1940 ; Barney
Lawson, M.R.C.S. ENG., L.R.C.P. LOND. 1934 ; Keir MacKessack Leitch, M.B.,
CH.B. UNIV. EDIN. 1942 ; David Michael Nepean Longridge, M.R.C.S. ENG.,
L.R.C.P. LOND. 1941 ; William Magauran, M.B., CH.B. UNIV. GLAS. 1935 ;
Keki Sorabji Masalawala, M.B., B.S. UNIV. BOMBAY 1940 ; Nevil Robert
Kennedy Mitchell, M.B., CH.B. UNIV. EDIN. 1943 ; Mary Genevieve Murphy,
M.B., B.S. UNIV. LOND. 1937 ; Ian William James McAdam, M.B., CH.B. UNIV.
EDIN. 1940 ; Lawrence Ruhal Rabson, M.D. UNIV. MANITOBA 1936 ; Derek
Raymond Ryder, M.B., CH.B. UNIV. NEW ZEALAND 1937 ; Ronald Swanson
Stewart, M.B., CH.B. UNIV. NEW ZEALAND 1932 ; Ernest Bruce Tovee, M.D.
UNIV. TORONTO 1938.

Royal College of Surgeons of Edinburgh

Henry Arthur Dalziel Ferns Bursary.—The Henry Arthur Dalziel Ferns
Bursary was, after a competitive examination in organic chemistry in its
application to medicine, awarded to Mr Ian S. Trotter.

NEW BOOKS

The Autobiography of David ——. Edited by ERNEST RAYMOND. Pp. 168.
London : Victor Gollancz. 1946. Price 7s. 6d.

This book, written for the general public, has been arranged from autobiographical
material by a well-known author. It describes the life and struggles of a man who
was afflicted with agoraphobia and uncontrollable compulsions. His weaknesses
landed him in the hands of the police and in various mental hospitals. These
experiences are described from the point of view of one who was not insane. The
writer has nothing hard to say about the medical profession but makes a plea for a
better understanding of mental ill-health. This exposition of the patient's point of
view should appeal to all medical men.

The March of Medicine in Western Ontario. By EDWIN SEABORNE, M.D., F.A.C.S.,
LL.D. Pp. xvi+386, with 112 illustrations. Toronto : The Ryerson Press,
(Price not stated.)

This is an interesting addition to the local history of medicine in Western Ontario,
compiled as a result of laborious research among a great mass of old documents
rescued from the Tower room of the Court House of London (Ont.) and from extensive
personal inquiries. It deals with the gradual evolution of medical practice, and the
building up of hospitals and teaching institutions in the province through the three
periods of Canadian history—Indian, French and English. Much of the text is of
purely local interest, but with the illustrations by Stanley Dale, a clear and interesting
picture emerges.

Rare Diseases and some Debatable Subjects. By F. PARKES WEBER, M.D., F.R.C.P.
Pp. 174. Illustrated. London : Staples Press. 1946. Price 15s. net.

Dr Parkes Weber has a wonderful knowledge of rare and out-of-the-way conditions,
and his contributions at medical societies always commanded respectful interest.
He has also been very prolific as a writer. The present book is a collection of short
articles which have already appeared in various journals. Dr Parkes Weber not only
describes his own experience but compares his cases with others published in the
literature.

This interesting volume should appeal not only to the specialist in medicine but
also to the general practitioner.

Structure and Functions of the Human Body. By R. N. BAILLIF, PH.D., and
D. L. KIMMEL, PH.D. Pp. xii+328, with 158 illustrations. London : J. B.
Lippincott. 1945. Price 18s.

The authors admit that there are already many good textbooks in Anatomy and
Physiology, but suggest that these are too voluminous for efficient use in the time
allotted to an introductory course, so that the student will accumulate a mass of
isolated facts without appreciating the significance of the field as a whole. The
present book has been planned to meet this difficulty. A book of this sort hardly
seems necessary for students of medicine, but would make an admirable textbook
for nurses and others who require a more general knowledge of these subjects.

A Charter for Health. Pp. 95. Illustrated. London : George Allen and Unwin.
1946. Price 6s. net.

A committee of experts under Sir John Orr has produced this book for the British
Medical Association as a comprehensive statement of the views of the medical
profession on the basic principles of health. Controversial issues have been carefully
avoided but the text covers a wide field and discusses many problems. It points
out that good health is not merely a question of medical services, but is largely
determined by good housing, adequate feeding, proper sanitation, favourable
conditions at work, facilities for recreation and education.

The book is simply written for the layman. It marshals facts, points out conclu-
sions and suggests lines for improvement. It is interestingly written and beautifully
illustrated and it should serve a useful purpose.

Die verteilung der Sulfonamide im Organismus. By PAUL EGGER. Pp. 113.
Helvetica Medica Acta Series A. Suppl. 17. Vol. 12, 1945.

This book contains a fairly complete review of work on the fate of sulphonamides
in the body with a bibliography of 320 references, and a number of new observations
by the author. Working in Switzerland, he considers that the most important
sulphonamides are sulphathiazol, sulphadimethyl-pyrimidine and dimethylbenzoyl
sulphanilamide (Irgafen) and he has chosen these for detailed study. Irgafen has a

high concentration in the serum compared with the cells and is retained longer in the body than the other two drugs. The drugs probably combine with serum albumin, and when this is low (in nephrosis) they are excreted more rapidly than normal. Most tissues contain less of all three drugs than the blood. The significance of these and other such facts is discussed. This work is a valuable contribution to the theoretical study of these drugs.

Injuries of the Knee Joint. By I. S. SMILLIE, F.R.C.S. (ED.) Pp. xi+320, with 350 illustrations, 14 in colour. Edinburgh: E. & S. Livingstone Ltd. 1946. Price 35s. net.

War brings its excesses in many fields. To Mr Smillie it presented in the short space of five years a spate of knee injuries that would have submerged many a surgeon. But to have treated them, photographed them, tabulated them, and at the same time produced a book about them, reveals industry which can arouse only unqualified admiration. The first third of the book concerns meniscus injuries, and in it the author records, with clarity and common sense, the lessons learned from the operative removal of 1133 menisci, and sweeps away many of the cobwebs which enshrouded the teaching on this subject. Few will find cause to argue with his statements. The section on ligament injuries is more contentious and his enthusiasm for substitution procedures which ignore the vital physiological rôle of a ligament may evoke some criticism. In the remaining third of the book he deals with many less common injuries and has much that is new to offer. Throughout he is interesting and stimulating. The photography is a notable achievement, and the excellent illustrations are a striking feature of a most attractive book, which should be of great value to all those concerned with traumatic surgery.

NEW EDITIONS

Synopsis of Obstetrics and Gynæcology. By A. W. BOURNE. Ninth Edition. Pp. viii+500, with 168 illustrations. Bristol: John Wright & Son Ltd. 1945. Price 21s.

The ninth edition follows the same general lines as its predecessors. By tabulation it sets out in a clear and concise manner essential facts, as well as generally accepted present-day opinion, so as to aid revision by undergraduates preparing for examination in these subjects. Alterations have been made, but the author states that were it not for the " fixing " of teaching by the demands of examiners revision would have been more radical. The small line drawings should prove useful illustrations of essential points in pathology, diagnosis and treatment. As before, this small volume can be confidently recommended to students, for it contains an amazing amount of compressed but reliable information.

Text-book of the Practice of Medicine. By various Authors, edited by F. W. PRICE, M.D., C.M., F.R.C.P. Seventh Edition. Pp. xlv+2034, with 91 illustrations. London: Oxford University Press. 1946. Price 42s. net.

Price's well-known text-book has a considerable tradition behind it, and the present edition maintains the high standard of its predecessors. Some new contributors have given their assistance and there are a large number of changes in the text. Many of these are of a minor character but some parts have been completely re-written. A number of new articles have also been included.

This work is so outstanding that few practitioners will feel justified in being without a copy.

Clinical Parasitology. By CHARLES FRANKLIN CRAIG and ERNEST CARROLL FAUST. Fourth Edition. Pp. 871, with 305 engravings and 4 coloured plates. London: Henry Kimpton. 1945. Price 50s. net.

The present edition of this well-known book more than maintains the standard of the previous editions. It has been thoroughly revised and brought up to date A new chapter has been added on the "Geographical Distribution of Parasitic Infections," to show the effects of climate, temperature, prevailing winds, etc. Also, under each parasite is given a note as to its pathogenesis.

Experience gained in the recent world war is reflected in the descriptions of " Scrub Typhus " ; also the new methods of prevention and treatment of infestation by ecto-parasites by means of D.D.T. are described. In Section V is given a " Technical Appendix " which includes much useful practical information on methods of collecting, preparing and identifying protozoa, helminths and arthropods. There are also tables of diagnostic criteria for parasitic diseases, while other tables give the treatments recommended for the more important infestations.

The book is well produced and the illustrations are well chosen and informative, the diagrammatic representation of the life-cycles of many of the parasites being particularly useful.

The Vitamins in Medicine. By F. BICKNELL, D.M., M.R.C.P., and F. PRESCOTT, M.SC., PH.D., M.R.C.S. Second Edition. Pp. xii+916, with 208 illustrations. London: William Heinemann Ltd. 1946. Price 50s. net.

Considerable advances have been made during the three years which have elapsed since the first edition appeared, and these have necessitated much re-writing of the text.

The book gives an excellent account of present-day knowledge of the vitamins and is full of a wealth of information. For those who wish to consult original papers, a full bibliography is given at the end of each chapter. The total references now number well over 4000.

This work can be regarded as an authoritative account of the subject.

Disinfection and Sterilization. By ERNEST C. McCULLOCH. Second Edition. Pp. 472, with 68 engravings. London: Henry Kimpton. 1945. Price 33s. net.

This book might be described as an encyclopædia of information about germicidal agents of all kinds, beginning with natural agencies such as sunlight and evaporation, going on to the anti-bacterial powers of the body, to radiant energy emanations, and the use of heat, cold, electricity and chemical agents of all kinds. The dynamics of disinfection and the mode of action of different agents are discussed.

The practical use of germicides in the laboratory, in medicine and surgery, water purification, sewage treatment, dairy methods, and in trades and domestic work is described in detail.

It is full of useful information for bacteriologists, public health workers, and medical men generally.

Notable Names in Medicine and Surgery. By HAMILTON BAILEY, F.R.C.S., and W. J. BISHOP, F.L.A. Second Edition. Pp. viii+202, with many illustrations. London: H. K. Lewis & Co. Ltd. 1946. Price 15s. net.

A very short time has elapsed since we welcomed the first edition of this little book. Few changes have been made in the present edition. The object of the book is to give a thumb-nail sketch of those illustrious practitioners whose names are remembered by instruments or procedures they introduced. Each story is accompanied by a portrait and often by a further illustration. The book is excellently produced and should be of interest to every practitioner of medicine or surgery.

BOOKS RECEIVED

BABCOCK, WAYNE, M.D. Principles and Practice of Surgery.
Henry Kimpton, London   60s. net.

BAILEY, HAMILTON, F.R.C.S., F.I.C.S., and R. J. McNEILL LOVE, M.S., F.R.C.S.,
F.I.C.S. A Short Practice of Surgery. Seventh Edition.
(H. K. Lewis & Co. Ltd., London)   40s. net.

BELL, ARTHUR C. H. A Pocket Obstetrics.
(J. & A. Churchill Ltd., London)   7s. 6d. net.

BONNEY, VICTOR. The Technical Minute of Extended Myomectomy and
Ovarian Cystectomy. . . . . *(Cassell & Co. Ltd., London)*   30s. net.

By a Committee of the British Medical Association under the Chairmanship
of Sir John Boyd Orr. A Charter for Health.
(George Allen & Unwin Ltd., London)   6s. net.

DAVIS, DAVID M., M.D. Urological Nursing. Fourth Edition.
(W. B. Saunders Company, London)   12s. net.

DENSFORD, KATHARINE J., M.A., R.N., D.SC., and MILLARD S. EVERETT, PH.D.
Ethics for Modern Nurses . . *(W. B. Saunders Company, London)*   9s. net.

ELLIS, E. S., M.R.C.S., F.R.A.I. Ancient Anodynes.
(William Heinemann (Medical Books) Ltd., London)   21s. net.

GRAYBEIL, ASHTON, M.D., and PAUL D. WHITE, M.D. Electrocardiography in
Practice. Second Edition . . *(W. B. Saunders Company, London)*   35s. net.

GREAVES, JOSEPH E., M.S., PH.D., and ETHELYN O. GREAVES, M.S., PH.D.
Elementary Bacteriology. Fifth Edition.
(W. B. Saunders Company, London)   20s. net.

HEMMELER, G. L'Anemie Infectieuse.
(Benno Schwabe & Co., Verlag, Basle)   —

HILL, H., F.R.SAN.I., F.S.I.A., A.M.I.S.E., and E. DODSWORTH, M.R.SAN.I.,
M.S.I.A. Sanitary Science Notes . *(H. K. Lewis & Co. Ltd., London)*   7s. 6d. net.

LOMHOLT, SVEND, M.D., O.B.E. Venereal Diseases in General Practice.
(H. K. Lewis & Co. Ltd., London)   25s. net.

LUDWIG, EUGEN. Die Periphere Innervation.
(Benno Schwabe & Co., Verlag, Basle)   —

MARSHALL, CLYDE, M.D., and Revised by EDGAR L. LAZIER, PH.D. An
Introduction to Human Anatomy. Third Edition.
(W. B. Saunders Company, London)   12s. 6d. net.

MOLESWORTH, H. W. L., F.R.C.S. Regional Analgesin. Second Edition.
(H. K. Lewis & Co. Ltd., London)   8s. 6d. net.

OLSON, LYLA M., R.N. Prevention, First-Aid and Emergencies.
(W. B. Saunders Company, London)   15s. net.

Compiled by RALSTON PATERSON, MARGARET TOD and MARION RUSSELL.
The Results of Radium and X-ray Therapy in Malignant Disease.
(E. & S. Livingstone Ltd., Edinburgh)   7s. 6d. net.

Edited by RAYMOND, ERNEST. The Autobiography of David ——.
(Victor Gollancz Ltd., London)   7s. 6d. net.

SEMON, HENRY C. G. An Atlas of the Commoner Skin Diseases. Third
Edition . . . . . *(John Wright & Sons Ltd., Bristol)*   50s. net.

SHORT, A. RENDLE, M.D., B.S., B.SC., F.R.C.S. The Causation of Appendicitis.
(John Wright & Sons Ltd., Bristol)   10s. net.

SKINNER, EUGENE W., PH.D. The Science of Dental Materials. Third
Edition, Revised . . . *(W. B. Saunders Company, London)*   24s. net.

STEVENSON, R. SCOTT. Morell Mackenzie.
(William Heinemann Ltd. (Medical Books) Ltd., London)   15s. net.

WHITBY, Sir LIONEL E. H., C.V.O., M.C., M.A., M.D., F.R.C.P., D.P.H., and
C. J. C. BRITTON, M.D., D.P.H. Disorders of the Blood. Fifth Edition.
(J. & A. Churchill Ltd., London)   30s. net.

WILLIAMS, JESSE FEIRING, M.D., SC.D. Personal Hygiene Applied. Eighth
Edition . . . . . *(W. B. Saunders Company, London)*   12s. 6d. net.

ZIMMER, E. A. Die Durchleuchtungstechnik der Thoraxorgane.
(Benno Schwabe & Co., Verlag, Basle)   —

THE SURGICAL PATHOLOGY OF PEPTIC ULCER AND GASTRIC CARCINOMA *

By JOHN MORLEY, Ch.M., F.R.C.S.

Professor of Surgery, University of Manchester

THE great frequency of gastric and duodenal ulcer can be realised if we recall that in a consecutive series of 4000 post-mortem examinations on patients of all ages carried out by Matthew Stewart (1931) at Leeds, some 10 per cent. showed the presence of either active peptic ulcer or the scars of old ulcers.

ETIOLOGY

Although there is much that is mysterious about the causation of peptic ulcers, the importance of acid gastric juice in their production is obvious when we consider their distribution. The first part of the duodenum, where the acid chyme impinges on its anterior wall, is the most frequent site. Next comes the lesser curvature of the stomach, which is in the closest contact with both food and active gastric juice. Anastomotic and jejunal ulcers are formed where a gastro-enterostomy has subjected the susceptible jejunal mucosa to the digestive action of the gastric juice ; and rarest and most dramatic of all, we find the peptic ulcer high above the diaphragm in association with a congenital short œsophagus, or low in the ileum when an ectopic area of gastric mucosa occurs in a Meckel's diverticulum. One does find a small minority of cases in which a chronic gastric ulcer is associated with complete absence of hydrochloric acid in the fractional gastric analysis, even after injection of histamine, but this does not necessarily mean that there had been a complete achlorhydria at the time of the formation of the ulcer.

We have to realise that a great change in the sex distribution of these ulcers took place during the early years of the present century. When I was a student from 1903 to 1908, the medical wards contained large numbers of pale anæmic young women with epigastric pain and a history of hæmatemesis. This chronic gastric ulcer of adolescent girls, associated with a chlorotic or microcytic type of anæmia, has

* Guest lecture in Surgery delivered at the University of Edinburgh on 12th March 1946.

practically disappeared, but in its place we have seen a remarkable steady increase in the frequency of duodenal ulcers in men. This will be appreciated best by some statistics published by Jennings in 1940 (Figs. 1 and 2). Various environmental causes have been suggested for this change, such as the abolition of tight lacing and improvement in the female dietary, but the real reason is quite obscure, and no one has accounted for the increase in duodenal ulcer in men.

Much time has been spent by pathologists in a search for a local devitalising agent on which could be laid the blame for allowing the gastric juice to start the erosion or ulceration of the mucosa. Various authorities have postulated septic infection and ulceration of the
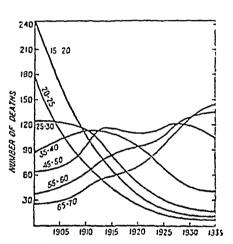
FIG. 1.—Annual deaths from peptic ulcer in females in certain selected five-year age-groups. From the statistics of the Registrar-General. (From Jennings (1940); by kind permission of *The Lancet*.)
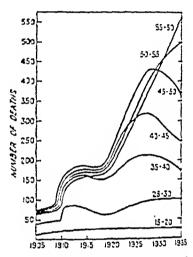
FIG. 2.—Annual deaths from peptic ulcer in males in selected five-year age-groups. From the statistics of the Registrar-General. The sudden rise in 1911 is due to the inclusion (for the first time) of deaths from duodenal ulcer. (From Jennings (1940); by kind permission of *The Lancet*.)

lymphoid follicles in the submucosa, or a local vascular thrombosis. Remote septic foci in the teeth or tonsils have received concentrated attention, sometimes with benefit to the patient, but many a good set of teeth has been sacrificed on the altar of an unproved theory.
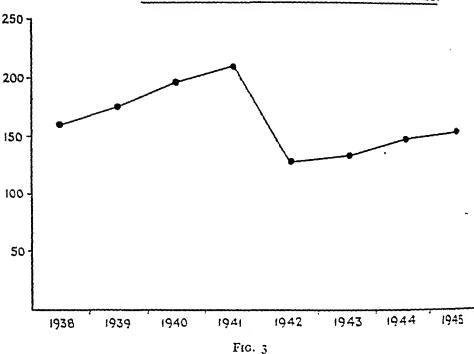
It was Harvey Cushing (1932), the great neurosurgeon, who first focussed attention on the influence of the central nervous system in the formation of peptic ulcers. The occurrence of acute perforated duodenal ulcers and the death from peritonitis of the patient within four days of the removal of a cerebellar tumour, recalled to his memory another case with perforation of multiple acute gastric ulcers that had happened in his practice twelve years before, after a similar operation, and led him to suspect that there might be a direct causal relationship between the operation on the cerebellum and the formation of the peptic ulcers. In 1932 Cushing published his classical paper on peptic

ulcer and the interbrain, in which he marshalled a mass of evidence, both clinical and experimental, for the view that a higher parasympathetic centre in the hypothalamus controls gastric secretion and motility through the vagus nerves. He showed that the neurogenic theory of the causation of peptic ulcer first conceived by Rokitansky, may be harmonised in this way with Virchow's theory of a local vascular lesion in the stomach or duodenum.

While I believe that Cushing's work threw a flood of light on this hitherto obscure problem, we must not suppose that stimuli originating in the hypothalamus are the sole cause of peptic ulcer. Somervell (1942) and McCarrison (1931) have shown that in certain districts of S. India the extreme frequency of peptic ulcer must be due to deficiencies in diet, and probably of vitamins A and B_2. But in Europe and America the view has gained ground steadily that to emotional influences, and in particular to prolonged worry, can be attributed a main part in the causation of peptic ulcers. The hypothalamus, as you know, is the seat of the expression of the emotions, and probably controls also the parasympathetic and sympathetic systems. Why it is that, subject to the strain of some depressing emotion, one individual will develop a peptic ulcer, another a toxic goitre, ulcerative colitis, hypertension or an anxiety neurosis, or just endure the strain without developing any of these maladies, remains one of the many unsolved problems of this supremely interesting field of psychosomatic relationships.

It is undoubtedly true that during the recent war there has been a marked increase in the incidence of peptic, and particularly of duodenal ulcers. Acute perforations are a convenient index of this trend, as they are, broadly speaking, all operated on and the diagnosis is not in doubt. Spicer *et al.* (1944) have shown the increase in perforations in London, and Rendle Short (1942) in Bristol. Fig. 3 shows the curve of perforated ulcer in the three largest Manchester hospitals during the war. Illingworth and others (1944) have ascertained the number of perforated peptic ulcers that occurred in the Glasgow district in the twenty years, 1924-43. As can be seen from Fig. 4, there is a more or less steady rise up to 1939 and then a remarkable increase in 1940 and 1941, with a drop in 1942 and 1943 to the pre-war level. The rise is almost entirely due to duodenal perforations. It might be supposed at first sight that the air raids on Glasgow provided the emotional cause for this remarkable increase in perforations, but Illingworth has pointed out that the peak of the curve in March 1941 preceded the two big air raids. It cannot be attributed to dietary deficiencies for two reasons. First, throughout the war the diet of all classes was very uniform under our rationing system, and did not vary from year to year. Secondly, the working classes, in whom the great majority of duodenal perforations occur, were on the whole provided with a better balanced and more nourishing diet than before the rationing period. Undoubtedly, the air raid alarms and home

PERFORATED ULCERS IN 3 MANCHESTER HOSPITALS.

FIG. 3
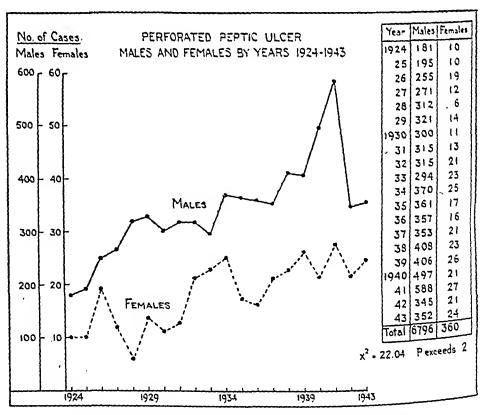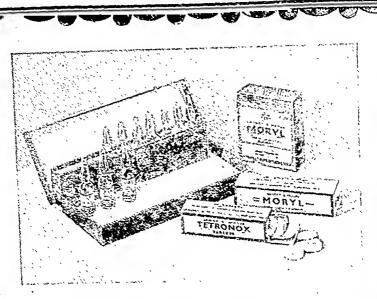
FIG. 4.—(From Illingworth *et al.* (1944) ; by kind permission of the
British Medical Journal.)

guard duties at night, with consequent loss of sleep, were important factors, and there was some easing off in that respect after 1941. But I would suggest as another possible explanation of these remarkable curves the gloomy situation in which we found ourselves in 1940-41 when we stood alone against the Axis. After the folly of Hitler in June 1941 had brought Russia into the war, and still more after Japan's attack at Pearl Harbour in December 1941, it was no longer possible to believe that Germany could win the war. I suggest that the happier emotional atmosphere that followed this change in our prospects was the main cause of the remarkable drop in perforations to the pre-war level.

The Relation of Gastric Ulcer to Cancer

I turn now to a subject on which controversy has raged for many years : the frequency with which cancer originates in a simple chronic gastric ulcer. The problem is limited to gastric ulcer, since duodenal ulcers never become malignant, and cancer in the duodenum, apart from ampullary carcinoma in the second part, is so rare as to be a pathological curiosity.

In 1909 Wilson and MacCarty startled the medical world by a paper in which they claimed that 68 per cent. of a series of chronic gastric ulcers excised as such at the Mayo Clinic showed evidence of early carcinoma on microscopical section, and that 71 per cent. of a series of gastric cancers showed microscopical evidence that they had originated in a previous chronic ulcer. If these figures were true, it meant that the main cause of gastric cancer had been discovered, and that its prevention demanded the excision of all gastric ulcers with the least possible delay. No wonder that many surgeons were at first inclined to hail with enthusiasm this new argument for war to the knife against cancer. But when the matter was investigated in this country no support for the new theory was forthcoming. Dible (1925) examined a consecutive series of 126 chronic gastric ulcers removed by various Manchester surgeons, and found no evidence of malignant change in any of them. In 33 gastric cancers he found only two which might have originated in a previous chronic ulcer. In a clinical investigation I found (1923) that in a series of 54 cases of proved cancer the average duration of gastric symptoms before the operation was 12·7 months, whereas in 45 cases of proved chronic ulcers the average duration of symptoms was 10·3 years.

It was Spilsbury (1921) who first drew attention to the fallacy that had led Wilson and MacCarty astray. He pointed out that at the edge of a chronic ulcer we often find areas of distorted epithelium dragged down by scar tissue below the level of the muscularis mucosæ, and showing irregularities in the alveolar formation very suggestive of early malignancy though in fact they are quite benign. These epithelial distortions were undoubtedly regarded by the Mayo Clinic

pathologists as early carcinoma. Other pathologists have carried out investigations into this problem with results not widely differing from Dible's. Stewart (1931) found 6·1 per cent. of carcinomas in a series of 277 chronic gastric ulcers removed at operation, and in 109 operation specimens of cancer of the stomach he found 15·6 per cent. that showed some evidence of having originated in a pre-existing simple ulcer. Newcomb (1932) found that 3·75 per cent. of chronic gastric ulcers showed early malignant change and that 13 per cent. of cancers gave evidence of previous peptic ulceration.

It must be observed that it is far more difficult to be sure that a carcinoma was preceded by a simple ulcer than to identify early cancer in a simple ulcer, because the scirrhous type of cancer produces fibrosis that may well be mistaken for evidence of simple ulcer, and I believe that both Stewart and Newcomb have somewhat exaggerated the frequency with which traces of previous ulcer can be found in established cancers. One of my reasons for believing that cancer rarely arises in a chronic ulcer is found in the hour-glass stomach, which is produced by very old-standing ulcers commonly of fifteen or twenty years' duration at least. These hour-glass stomachs are found almost invariably in women—a fact which is attributable to the long slender J-shaped stomach of the female as contrasted with the short broad stomach of the male ; but the remarkable thing about them is that they are almost invariably non-malignant. Whenever an hour-glass stomach proves to be malignant we find that there is a short clinical history which means that it was malignant from the first. But this applies only to some 2 per cent. of hour-glass stomachs. If the irritation of a chronic ulcer were a common cause of cancer, it is here, in this special group of hour-glass stomachs with their exceptionally long history, that we should naturally expect to find the highest proportion of ulcer-cancers. The fact that cancer is so rare in this group gives us good reason to believe that a malignant change in chronic ulcer is most unusual.

There are two clinical fallacies underlying the common belief in the malignant degeneration of ulcers. One is that a cancer of the stomach may start in some part of the stomach remote from the ulcer and so may be quite independent of the ulcer. On three occasions when operating on a cancer of the stomach with an unusually long history of indigestion, I have found, in addition to the growth, an old duodenal ulcer that explained the long history. Fig. 5 shows the stomach of a woman with a fifteen years' history of ulcer and a six months' history suggesting pyloric stenosis. There is a cancer of the pylorus, probably of six months' standing, and separate from it a chronic ulcer which explains the fifteen years' history. Had the operation been delayed until the growth had reached as far as the ulcer, one would have been tempted to say here is a cancer that started in a chronic ulcer. Incidentally, that woman is alive and well eighteen years after her gastrectomy. The other fallacy is still more important

and consists in the difficulty of diagnosing between ulcer and cancer. It is not realised sufficiently how slow in their growth some cancers of the stomach may be, or how closely they may simulate clinically a simple chronic ulcer. We are all familiar with the very slow-growing atrophic scirrhus of the breast, which after five or ten years may still be quite small and may not yet have caused metastases. Although most cancers of the stomach run their course within two years, it is not uncommon to find one that has been present three, four or five years, producing symptoms simulating ulcer although it has been
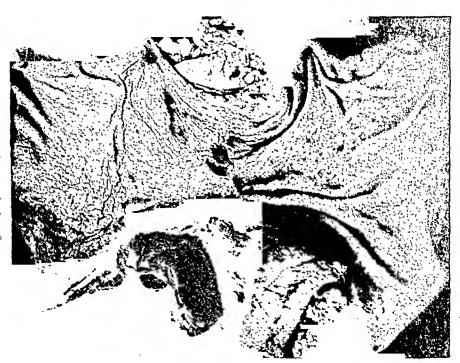
FIG. 5.—Stomach opened out to show both carcinoma of pylorus and chronic peptic ulcer.

in reality a cancer from the first. Let me tell you of a cancer of the rapid type that simulated ulcer radiologically though not clinically. The patient was a lady, aged sixty, with a two months' history of indigestion. The first X-ray showed what appeared to be a simple penetrating ulcer of the lesser curvature. Medical treatment by diet, rest and alkalies caused marked relief of symptoms, and after six weeks another X-ray showed the ulcer apparently healed. After a further four months she was again losing weight and having pain, and a third X-ray, taken only seven months after the onset of symptoms, showed an extensive carcinoma, which, on exploration of the abdomen, proved to be inoperable. It must have been a cancer from the first, and the appearance of healing was due to the efficient medical treat-

ment which had neutralised the gastric juice so that the cancer cells were no longer digested.

The conclusion I come to is that a malignant change in a gastric ulcer is a rare pathological curiosity, and I do not believe it occurs in more than 1 or 2 per cent. of cases. In my series I could find only one convincing case of cancer originating in ulcer, and even here there is a doubt, because the pre-operative history was only two years in duration.

GASTRIC CARCINOMA

The stomach is the commonest site of cancer in the body, and gastric cancer causes the death of well over 12,000 people in these islands every year. It is commoner in men than women in the proportion 6 : 5.

We may classify cancers of the stomach according to their gross naked eye features as ulcerating, polypoid or fungating, colloid and leather bottle cancer. Or again we may base our classification on the microscopic appearance as adeno-carcinoma, which may be columnar or spheroidal-celled, carcinoma simplex, colloid and anaplastic forms. Neither of these classifications is very satisfactory, however, since they cannot be correlated with the clinical symptoms, and, further, the various types often merge into one another in an indefinite way. From the clinician's standpoint it is better to classify them as cancer of the pyloric end, of the body of the stomach and of the cardiac end, as cancers in these three portions give rise to such different symptoms.

Etiology.—What do we know of the cause of cancer of the stomach ? We have seen already how little ground there is for the widely held belief that a considerable proportion of cancers originate in simple chronic gastric ulcers.

There is another theory which we owe to the late Sir Arthur Hurst. Hurst (1929) held that, " The achlorhydria so commonly associated with cancer of the stomach is a result of chronic gastritis which precedes the onset of the carcinoma and is in fact the most common predisposing condition." He says, " I have never seen a case of carcinoma in which free hydrochloric acid was present at an early stage and disappeared as the disease advanced." He implied very plainly that if he had not seen such a case it was unlikely that anyone else had. However, in 1935, Robertson described such a case in which a series of fractional gastric analyses over a period of nine months showed a steady decline in HCl from the original high curve to a complete achlorhydria towards the end (Fig. 6). Fig. 7 shows a similar chart where the first test meal showed a fairly high acid curve and a second, four months later, showed complete achlorhydria. These charts, and they could be multiplied, plainly contradict Hurst's contention.

But further evidence on this point has recently come to light. In refutation of a statement by Kaplan and Rigler (1945) that pernicious
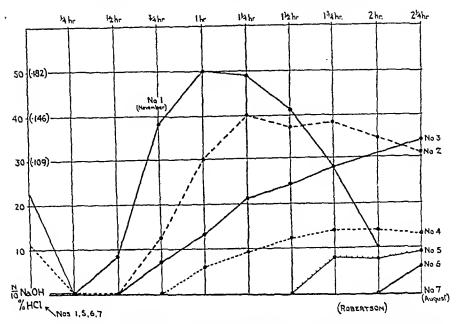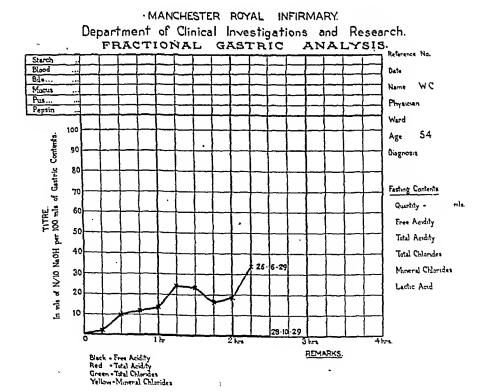
FIG. 6.—Curves of the secretion of free hydrochloric acid from November (No. 1) to following August (No. 7). (From Robertson (1935); by kind permission of *The Lancet*.)

FIG. 7

anæmia was a frequent predisposing cause of gastric cancer, my colleague Dr J. F. Wilkinson (1945) has stated that of 1600 consecutive patients with pernicious anæmia under his regular observation during the last seventeen years, only 28 (1·75 per cent.) developed cancer, and of these only 12 (6 males, 6 females) had cancer of the stomach. These 12 had been under observation for an average of seven and a half years, and 9 of them were over sixty years old when cancer was diagnosed. It is plain that if you took 1600 people of the same age group who were free from pernicious anæmia, and watched them for over seven years, you might expect as many as 12 to develop cancer of the stomach. Now 100 per cent. of patients with pernicious anæmia have this very form of atrophic gastritis with achlorhydria which Hurst regarded as the chief cause of gastric cancer. It is surely obvious that if Hurst's theory were true, a very high percentage of pernicious anæmia patients should develop gastric cancer. They lead a sheltered and controlled existence, with frequent visits to a hæmatological clinic, and no longer die of their anæmia, but their achlorhydria and atrophic gastritis remain in spite of their treatment. Wilkinson's figures provide, I think, a complete and final refutation of the theory that atrophic gastritis is a predisposing cause of cancer. The achlorhydria that one finds in some 70 per cent. of all patients with cancer of the stomach would appear to be the result of the cancer rather than its cause.

The fact is, and it is well to admit it, that we know next to nothing about the cause of cancer of the stomach. It always seems remarkable to me that the only cancers of which we have some indication of a cause are the comparatively rare ones. We know of the irritation of clay pipes in cancer of the lip, or of oil in cotton spinners' cancer of the scrotum ; of cancer of the skin in workers in tar, and of cancer of the bladder in workers with aniline dye. We know that cancer of the gall-bladder is due to the irritation of gall-stones. When we come to the common cancers, those of the stomach, of the breast, of the colon and of the rectum, we do not find any clue to the riddle. The great majority of patients with cancer of the rectum have never suffered from constipation or colitis. Cancer of the breast affects a previously healthy organ far more often than one that has suffered from chronic mastitis ; and cancer of the stomach usually affects a patient who has hardly ever known a day of indigestion before the symptoms of the fatal disease appear. It is the first condition of an advance into the unknown that we should recognise our ignorance and reject false theories.

The solution of this grievous problem of cancer, which weighs so heavily on humanity, will probably come from the biochemist, who has already pointed the way in the stilboestrol or castration treatment of cancer of the prostate. The treatment of that form of cancer by these therapeutic agents differs from all other cancer treatment, surgical or radiological, in this profoundly important respect, that

the secondary deposits are made to recede as well as the primary growth. But as regards the cause and cure of cancer of the stomach, we must admit that, at present, we see as in a glass darkly. Until the mystery is laid bare, let us realise that the only hope for a patient with gastric cancer lies in early diagnosis and prompt treatment by subtotal gastrectomy.

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THE USE OF ISOTOPES IN BIOLOGY *

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PRACTICALLY all the mass of an atom is concentrated in the nucleus and this is surrounded by a number of negative electrons whose mass is almost negligible compared with that of the nucleus. Atoms are very small things. The relation between the size of the solar system and the size of a man is about the same as the relation between the size of a man and the size of an atom. For example, if you took one-hundred thousand million men and put them end-to-end they would reach to the sun, and if you took the same number of fluorine atoms and put them end-to-end they would be about as tall as a man. In spite of their very small size, atoms are very empty. The nucleus is very small compared with the distance of the electrons. If someone made an enlarged model of an atom in which the nucleus was represented by a steel ball 1 cm. in diameter, then the average electron would be represented by a small balloon about 100 yds. away.

The nucleus consists almost entirely of protons and neutrons. A proton is the same thing as an atom of ordinary hydrogen. Its mass is practically equal to 1, on the usual scale, and it has one positive charge of electricity. A neutron has a mass of one and no charge. An electron has practically no mass and one charge. It has been suggested that a neutron really consists of a proton combined with a negative electron so that the electric charges are neutralised. This theory seems, at first sight, to be supported by the fact that it often happens during radioactive decay that a neutron becomes converted into a proton in the nucleus and a negative electron is thrown out in the process ; but unfortunately, the facts are not so simple, since a proton may be converted into a neutron and give off a positive electron in the process. It often happens that the behaviour of atoms fails to conform with what we have come to regard as the dictates of common-sense.

The chemical properties of an atom depend only upon the number of electrons which are attached outside the nucleus, the ones corresponding to the small balloons in the model. When the atom is electrically neutral this number must be equal to the number of protons in the nucleus. Chemical properties are thus controlled by the number of protons. The atomic number of an element is equal to the number of protons in its nucleus. Hydrogen has one proton and its atomic number is 1. Uranium has 92 protons and its atomic number is 92. All the other natural elements have an intermediate

* A lecture to postgraduate students.

number of protons and intermediate atomic numbers. Recent work on atomic bombs has led to the synthesis of two new elements, neptunium and plutonium whose atomic numbers are 93 and 94. These large atoms are all of them unstable. In fact, all atoms with atomic numbers larger than 83, which corresponds to bismuth, are unstable.

All elements, except hydrogen, also have neutrons in their nucleus. In fact, with one other exception, all stable nuclei have at least as many neutrons as protons.

Two elements are said to be isotopic with one another when they have the same atomic number and the same chemical properties but different atomic weights. That is, the same number of protons but a different number of neutrons. The simplest isotope is heavy hydrogen which consists of one neutron and one proton. It has the same chemical properties as ordinary hydrogen, but about double the weight. Heavy hydrogen is sometimes called deuterium and a single atom of it is sometimes called a deuteron. Several hundred new isotopes have been manufactured in the last few years, and these new isotopes either contain too many neutrons or too few neutrons compared with the natural elements. These new isotopes are made by bombarding ordinary atoms with small particles travelling at high velocities. Owing to the very small size of the nucleus it is difficult to hit it and a lot of the missiles are wasted. The production of particles travelling with sufficient velocity to produce definite changes in the nucleus is rather difficult. When the particles contain an electric charge they can be accelerated by exposing them to large voltages, but the voltages required for this purpose are of the order of a million or more, if the acceleration is all done at once. It is more efficient to make the particles travel round in circles in a cyclotron and accelerate them by exposing them to a series of voltage changes so that their velocity is gradually increased up to the required value. The particles which are used in a cyclotron may be protons or deuterons or alpha particles. Each alpha particle consists of two protons and two neutrons.

The most important other form of missile is the neutron. These cannot be accelerated electrically because they have no electric charge and they can only be derived by the break-up of atoms. Neutrons are very efficient missiles because, having no charge, they find it comparatively easy to penetrate the nucleus. In the last few years, as a result of work on atomic bombs, neutrons have become much more readily available. The break-up of atoms liberates large numbers of neutrons and these then break up other atoms so that the process propagates itself and may either go on for a long time, or else produce a very large explosion.

When a small particle hits the nucleus of an atom all sorts of things may happen. It may just be captured and incorporated in the atom. It may be partly captured. For example, if the particle is a deuteron the neutron which it contains may be captured and the proton may escape. The missile may knock off part of the original nucleus, or if the

original nucleus is a large and unstable one, such as uranium, it may be broken up by the impact into quite large bits and all sorts of isotopes may be liberated. In any case, the nucleus is liable to be very much altered by the impact and the resulting nucleus may easily have a different number of protons or neutrons from the original nucleus. The bombardment of atomic nuclei thus produces new isotopes.

Isotopes may either be stable or unstable. The stable ones occur under natural conditions and the ordinary elements as we used to know them sometimes consist of mixtures of two or more stable isotopes. This is the main reason why some of the atomic weights of the elements are not whole numbers. For example, the atomic weight of chlorine is about 35·5 and this is because it consists of a mixture of 75 per cent. of an isotope whose weight is 35 and 25 per cent. of isotope whose weight is 37. The actual estimation of these stable isotopes generally depends on the use of the mass spectrograph, which is a large and expensive apparatus in which the atoms are hurled through a vacuum at high speed and subjected to electrical and magnetic forces which separate out elements of different weights. In the case of heavy hydrogen an alternative method is available, since the hydrogen can be converted into water and its concentration determined by measuring the specific gravity of the water. Very ingenious and accurate methods have been invented for doing this.

Other isotopes are unstable and undergo spontaneous changes which eventually lead to the formation of stable forms of the atoms. Various radiations are thrown out in the process so that these atoms are artificially radio-active. The speed at which this happens is measured by the half-life which is the time it takes for half of the radioactive atoms to break up. It is measured by the rate of decay of the radioactivity. In one half-life this falls to half its initial value; in two half-lives it falls to a quarter; in three half-lives it falls to one-eighth, and so on. The half-life may vary from a small fraction of a second to many thousands of years.

The rays given off may be of various kinds and have been labelled α, β, and γ rays. Practically all radioactive elements give off β rays which consist of electrons which may be positive or negative, but the negative electrons are the commoner and more stable. The range to which these penetrate depends on the velocity at which they are ejected but is usually of the order of a few millimetres of water. Within this range each electron passes close to and through a very large number of atoms and so dislodges electrons from the outer rings of several thousand atoms. These dislodged electrons then get caught by other atoms so that each encounter causes the formation of a pair of electrically charged ions. Eventually, the original electron gets captured and its course comes to a sudden stop. Electrons projected from a given isotope are apt to have velocities varying fairly widely so that their ranges also vary over a fairly wide range.

A large proportion of radioactive isotopes also give off γ rays which may be regarded as electro-magnetic waves with very short wave length. They penetrate matter more easily than X-rays and each γ ray is gradually absorbed and its energy gradually falls off and it does not come to a sudden stop like an electron. α particles, which are identical with helium atoms and contain two protons and two neutrons, are only given out by some of the heaviest elements. Their practical importance nowadays is much less than might be supposed from the fact that the first letter of the alphabet has been allocated to them. A few of these heavy elements of course, also break up into very much larger pieces than α particles; for example, the atom of uranium 235 is liable to break up into large pieces giving off enormous amounts of energy and neutrons and dozens of new isotopes in the process. The discussion of these phenomena is, of course, very important but lies outside the range of the present lecture. Most isotopes do not emit anything heavier than an electron so that their atomic weight does not appreciably alter as they decay.

The estimation of radioactive isotopes depends on the ionisation produced by the β and γ rays which they give off. For example, they can be estimated by putting them near an electroscope in which the charge is shown by the position of a gold leaf. When the atmosphere about the gold leaf is ionised the charge disappears more rapidly. The assay depends more commonly upon a Geiger counter, which is a tube filled with a suitable gas and containing electrodes; a large potential difference is applied to the tube so that very little more is needed to make a current jump across between the electrodes. When a single β or γ ray passes through this apparatus the tube is discharged and then rapidly charges itself again. Special apparatus similar to a wireless set counts the number of times this happens and gives a very sensitive measure of the number of rays which have passed through the counter and thus of the number of radioactive atoms in the neighbourhood.

Consider now the application of the new tool which is provided for scientific investigation by isotopes. They have been used both in chemistry and biology. The artificial isotope has exactly the same chemical properties as the natural isotope. Once the two have been mixed together they cannot be separated by ordinary chemical processes and living organisms do not appear to be able to distinguish between them. For example, the proportion of heavy hydrogen in the water obtained from living organisms is the same as in all other water. Isotopes can only be separated again by physical apparatus such as a mass spectrograph. The presence of the unusual isotope thus serves as a label for the particular atoms which have been used experimentally. If the isotopes are radioactive the presence of radioactivity serves as a label in the same way. The elements are said to be " labelled " or " tagged " by the presence of the isotope. A great amount of work has been done with such labelled elements. They are

administered to animals or plants and then recovered from different organs or from different chemical fractions of the living organism so as to see what chemical changes those particular atoms have undergone in the meantime. For example, Schoenheimer carried out an experiment on rats which were fed on a constant diet. From a chemical point of view their diet remained constant throughout the whole experiment, so that the animals were in equilibrium and were not subjected to any experimental procedures except the addition to their diet of labelled substances in such small amounts that they could not possibly produce any changes in the rat. For example, the amount of fat in the fat depôts remained constant throughout the experiment and it would be reasonable to assume that nothing at all was happening to it. It might be supposed that the animal would use the fat in its diet as a food, and would have no need to disturb its reserve of fat in the subcutaneous depôts and elsewhere. In one experiment palmitic acid labelled with heavy hydrogen was added to the diet in amounts negligible compared with the amount of palmitic acid that was in the diet already. After eight days 44 per cent. of the heavy hydrogen which had been given was recovered from the fat depôts of the rat. A large proportion of this was in the form of palmitic acid, and that shows that there was a free exchange between the palmitic acid in the fat depôts and the palmitic acid of the diet. Some of the heavy hydrogen was in the form of other fatty acids, such as stearic acid and lauric acid and unsaturated acids. The body had evidently lengthened the chain of some of the molecules received from the diet, shortened others and desaturated others. In fact, all the fatty acids in the body appeared to be changing into one another with the exception of linoleic acid and linolenic acid. This was interesting because those two acids were already known to be ones which the body was unable to make and which had to be supplied as such in the diet in order to maintain the animal's health.

A large number of different types of experiments have been done with labelled elements in this way. Both stable and unstable isotopes can be used. One advantage of using stable isotopes is that the materials do not decay during the experiment. Experiments with those radioactive isotopes which decay rapidly are sometimes very difficult because it is necessary to make the isotope and complete the experiment within a few minutes or hours. Another advantage of stable isotopes is that there is no danger that they will produce effects in the tissues due to their radioactivity. The methods of assay for the stable isotopes are very accurate quantitatively, but not very sensitive. The experimental possibilities may be limited by the fact that the stable isotope is already present in the body, and the labelled elements can only be measured when enough of them is used to produce a significant increase of the concentration normally present.

Radioactive isotopes are popular because the methods of assay are very sensitive and fairly simple, and the apparatus needed is

comparatively cheap. Radioactive isotopes also have various special applications which will be discussed later. The choice of isotope generally depends on what is available. The only suitable isotopes of oxygen and nitrogen are stable since the half-lives of the radioactive isotopes are extremely short. Hydrogen and carbon are generally used in the form of stable isotopes for the sake of convenience. Carbon has two radioactive isotopes, one of which, with an atom weight of 11 (C^{11}) has a half-life of twenty-one minutes, which is rather too short for most purposes, and the other (C^{14}) before long will become more easily available than it has been in the past and will have useful applications in biology. Meanwhile, a good deal of work has been done with C^{13} which is stable.

Much work has also been done in which carbon was labelled by attaching heavy hydrogen to it on the assumption that the label would not be dislodged. The experiments on fats have already been mentioned and are described in more detail in a fascinating book called *The Dynamic State of the Body Constituents*, by Rudolf Schoenheimer. This is based on the Dunham lectures given in 1941. It contains only sixty-five pages and is to be warmly recommended. It describes experiments on various other substances besides fats. Schoenheimer labelled amino-acids by using the heavy isotope of nitrogen (N^{15}). He found that the body proteins were constantly renewing their amino-acid from a common pool. This was true even of antibodies and of the proteins in tendons. In one experiment a rabbit was immunised to type III pneumococcus. After the immunising injections had stopped, and at a time when the amount of antibody in the blood was falling, the rabbit was given labelled glycine to eat. Blood was removed at intervals and the antibodies were precipitated with the specific antigen. This precipitate was found to contain just as much heavy nitrogen as the remaining blood proteins. It is very surprising that this specific protein should be turning over its glycine at a time when it was presumably no longer being produced and was gradually disappearing from the body. Schoenheimer also obtained evidence that amino-acids were not only being moved from protein to protein, but were also constantly renewing their own nitrogen from a common pool of ammonia. This was shown in experiments in which heavy nitrogen was given in the form of one amino-acid and recovered from another, or given as ammonia and recovered from the amino-acids. Glutamic acid and aspartic acid were particularly active in this way, but lysine took no part in these exchanges. He also did some interesting experiments in which lysine was doubly marked with heavy hydrogen and heavy nitrogen and given to rats. Lysine was then isolated from the rat's proteins and it was found that the labels were still present in their original proportion to one another. When similar experiments were done with leucine there was a relative loss of nitrogen, since some of this had been lost to the ammonia pool and transferred to other amino-acids.

Much work has been done with the radioactive isotope of phosphorus P^{32} (Hevesy 1940). When this is given as inorganic phosphate it rapidly disappears from the blood and is taken up by most tissues and converted into organic esters, phospholipids and other forms. The bones and teeth take it up rapidly and retain it for a long time. It penetrates even into parts of the teeth which have no circulation. For example, the tips of the incisors of rats were found to contain large amounts of radioactive phosphorus when the rats had been fed on radioactive phosphorus for a few days.

Hamilton (1942) points out that the amount of radioactive phosphorus obtained from any given tissue at any given time in experiments of this kind depends on various factors. It depends on the phosphorus content of the tissue. Tissues which are usually rich in phosphorus are likely to get more of the new phosphorus than tissues which are not. It depends on the turnover. Some tissues turn their phosphorus over quicker than others. For example, the liver turns over its phospholipids very rapidly and the C.N.S. turns over its phospholipids very slowly. It also depends on the growth of new tissue. Tissues which are growing rapidly need and take large quantities of any available phosphorus and incorporate this in nucleic acids, phospholipids and other essential structures.

Schoenheimer, in his book, lays great stress on the state of flux of the body. Even tissues regarded as structural are constantly being renewed. The old idea that the body is like a combustion engine which burns up the fuel it is given and only needs occasional repair is now out of date. Schoenheimer prefers to compare it with a regiment of soldiers. " A body of this type resembles a living adult organism in more than one respect. Its size fluctuates only within narrow limits, and it has a well-defined, highly organized structure. On the other hand, the individuals of which it is composed are continually changing. Men join up, are transferred from post to post, are promoted or broken, and ultimately leave after varying lengths of service. The incoming and outgoing streams of men are numerically equal, but they differ in composition. The recruits may be likened to the diet ; the retirement and death correspond to excretion."

Such facts were vaguely guessed before. The new evidence confirms and extends them in a very striking way and fills in a number of unexpected details. The characteristics of an individual do not depend on the material of which he is made, so much as on the organisation into which these materials are fitted.

Various interesting experiments have been done with radioactive iron. The absorption and fate of iron has long been rather a puzzle. There was evidence that the small intestine could readily absorb iron salts if these were given in a suitable form, nevertheless large quantities of iron were commonly found in the fæces. It was thought at one time that this fæcal iron had mostly been excreted in the large intestine and that the body controlled its iron content by controlling the

excretion. McCance and Widdowson (1938) found that the injection of iron did not increase the fæcal iron appreciably, and came to the conclusion that fæcal iron had passed right through the intestine without ever being absorbed and that the body controlled its iron content by controlling the absorption. Hahn and Whipple working with various collaborators obtained much other evidence in favour of this theory. They were more fortunate than McCance and Widdowson because they were able to use radioactive iron. In some experiments radioactive iron was estimated in the fæces. In other experiments the dogs were killed and the labelled iron was estimated in their tissues. Normal dogs absorbed less than 0·25 per cent. of the iron. Dogs which had just been bled absorbed about the same. Dogs which had been bled and then left until their reserves of iron had been used up to replace the hæmoglobin in the blood absorbed much more. The absorption of iron evidently depends on the body's reserves. It is interesting to note also that the iron soon appeared in the hæmoglobin.

Some interesting experiments have also been done in which labelled red-blood corpuscles were transfused. These red cells were obtained by giving radioactive iron to a patient and then removing his blood after a suitable interval and transfusing it into a second patient. The length of time that these cells remained in circulation could then be followed by measuring the radioactivity of the blood of the second patient. In one set of experiments two different isotopes of iron were used. These emit different kinds of radiation and can be estimated separately. It was thus possible to compare the effect of blood which had been freshly transfused with that of blood which had been stored before transfusion. Both bloods were given simultaneously to the same patient, and their fate was followed by estimating the two kinds of iron separately in the blood. Unfortunately, such experiments are complicated by the fact that when red blood corpuscles break up, the body uses their iron to make new cells. The evidence must therefore be interpreted with caution except in experiments of short duration. Incidentally, this technique provides a new and accurate method of determining the volume of the circulating blood by estimating the radioactivity of the blood immediately after the transfusion of radioactive cells. This can be measured twice and no more, since there are only two convenient isotopes.

In the experiments discussed so far, isotopes have been used as labels to distinguish atoms used by the experimenters from other atoms of the same kind already present in the body. Radioactive isotopes have various other applications depending upon their radioactivity.

One advantage of radioactive isotopes which is of particular interest to pharmacology is that they can be estimated in extraordinarily low concentrations. One of the main lines of advance in pharmacology at the present time is the study of the fate of drugs in the body by

estimating their concentrations in the blood and tissues. The sulphonamides, penicillin, and mepacrine, would have been much less successful drugs if it had not been possible to estimate their concentration in the blood, and to control the size and frequency of dose and the methods of administration in such a way as to produce and maintain an effective concentration in the blood, or at some local site of action. Some of the most active drugs produce their effects in such low concentrations that their estimation by ordinary chemical means is difficult or impossible. Various sensitive methods have been used. Penicillin is measured by biological assay ; mepacrine is measured by its fluorescence. Geiger counters can detect and measure very much lower concentrations than either of these methods and will no doubt have important applications in this way.

Radioactive isotopes should also be useful to those who study the *fundamental mechanisms of chemotherapy.* For example, when trypanosomes are treated with suitable organic arsenicals *in vitro* they are killed by very low concentrations. The drugs are taken up by the trypanosomes and disappear from the solution. Evidence for this depends on the fact that it can be shown under appropriate conditions that the solution has lost its lethal power when tested on a second sample of trypanosomes. The concentration is so low that it is impossible to study the process satisfactorily by estimating the arsenic by the ordinary chemical methods. It should now be possible to study the factors controlling the uptake of drugs by trypanosomes in a quantitative way.

In another type of experiment which probably has more interest for clinical scientists, radioactive substances are detected inside the living body by putting a Geiger counter near the body. This is only possible with isotopes which emit γ rays, since no other type of ray can penetrate a sufficient depth of tissue to be effective. For example, in one set of experiments a subject grasped the tube of a Geiger counter in his hand.· This was inside a lead box to protect it from radiations except those coming from his hand. He then swallowed radioactive salts of sodium, potassium, chloride, bromide or iodide. These substances were all absorbed rapidly so that the number of impulses in the counter showed an appreciable increase within a few minutes and reached a maximum in two hours. Potassium was taken up rather more slowly than the other elements. This technique clearly has many applications in the study of the uptake of all sorts of substances administered in all sorts of ways. It can also be used to study the circulation in the hand. If the circulation in one hand is much slower than in the other then there will be a difference in the rate of increase of radioactivity in the two hands. It should, however, be noted that these inorganic salts soon diffuse through the capillary walls so that the effect is not immediately and quickly reversible. A sudden stoppage of the circulation in the hand would not cause an immediate fall in the reading on the counter. It may be that the

circulation in the hand could be followed more accurately by using radioactive iron to label red-blood corpuscles. These would not escape from the blood vessels and the reading on the counter should give a direct measure of the amount of blood in the hands at any given moment.

Similar technique has been used to follow the rate of absorption of labelled insulin from a depôt. The Geiger counter was placed near the site of injection and the reading fell as the insulin was absorbed.

The most striking experiments which have been done with this technique were concerned with the uptake of iodine by the thyroid. The counter was placed over the thyroid and radioactive iodine was given. It has been known for some time that iodine is taken up by the thyroid in much higher concentrations than in other tissues. This fact was strikingly confirmed in these experiments. The administration of iodine had a large effect on the counter. After small doses it was estimated in some experiments that more than 50 per cent. of the dose appeared in the thyroid ; after larger doses the proportion was smaller. Abnormal thyroids had abnormal powers of concentrating iodine. In hypothyroidism, when the thyroid was small and inactive, it took up little or no iodine. In simple goitre, when the thyroid was enlarged but was causing no toxic symptoms, it took up more iodine than normal thyroids. In toxic goitre the uptake was larger still, but when large doses of iodine were given the iodine was not retained in the thyroid for more than a few hours. These observations may provide a clue to the interpretation of the effect of iodine in causing a temporary remission of the symptoms of toxic goitre. They may possibly also be of some diagnostic value. These experiments represent only one aspect of much work that has been done with radioactive iodine and the thyroid. For example, many interesting facts have emerged from the study of the radioactivity of the different substances which can be separated chemically in thyroid extracts.

Information has also been obtained by what is known as radio-autography or autoradiography. This is a very interesting technique with many applications. In these particular experiments, sections of thyroid gland containing radioactive iodine were placed in close contact with photographic films in a press. After a suitable period of exposure the films were developed and a picture was thus obtained showing the distribution of iodine in the tissue. The pictures obtained so far do not show fine details. Individual cells cannot be distinguished, but there is clear evidence that in active hyperplastic thyroids the cells contain little radioactive iodine. The colloid, which was, of course, small in amount in these hyperplastic thyroids, contained a rather large quantity of iodine, but some at least of the rest of the iodine had no doubt passed into the circulation as thyroxine and caused toxic symptoms. In simple goitre the colloid contained little iodine and the cells contained more. A carcinomatous growth of the thyroid did not accumulate iodine in anything like the same amount

as the normal thyroid tissue. There is clearly much to be done with this technique.

It remains to discuss the therapeutic use of radioactive isotopes. These can, of course, be used in the same way as radium and may possibly displace radium for this purpose. One of the isotopes of cobalt seems particularly suitable for use in this way. The possibility of treating disease by the injection of radioactive isotopes has also been studied in America. In certain cases it is possible to use preparations which are concentrated in certain tissues. It will be obvious from the previous discussion that it is possible to produce specific irradiation of the thyroid by the use of radioactive iodine. Other possibilities will be discussed later. Radium has been used in this way, but is unsuitable because of its expense and because it is retained in the bones and goes on irradiating the bone marrow during the whole of the rest of the patient's life, causing slow poisoning over a period of years. Radium is probably the most poisonous substance known. Isotopes with a short life are clearly safer to use. The isotope which has been most used in this way is radioactive phosphorus which has a half-life of 14·3 days (Low-Beer, Lawrence and Stone, 1942). When this is given as sodium phosphate the highest concentrations are found in the bones, but any tissue which is actively growing contains higher concentrations than tissues which are not. It has therefore been used to inhibit the growth of new tissues. Promising results have been obtained in the treatment of leukæmia, polycythæmia vera, and lymphocarcoma. There is no doubt that this treatment has a marked action on these diseases, but the clinical results are difficult to assess, and it is not yet possible to say whether it is better than older methods of treatment. It has been tried in Hodgkins' disease, multiple myelometa and in metastatic carcinoma. It is doubtful whether it had any good effect. The dose is limited by the fact that if too much is given the bone marrow is damaged and anæmia is produced.

Radioactive phosphorus has also been used in the form of chromic phosphate. This insoluble salt is given in suspension and is specifically concentrated in the reticulo-endothelial cells causing irradiation of the liver and spleen and bone marrow. It has been tried in the treatment of patients with metastatic new growths in the liver, but it is not yet clear if it is effective.

Radioactive calcium is concentrated in bone but its radioactive properties were not considered suitable for use in therapy. Radioactive strontium was therefore used instead. It behaves like calcium in the body and has been used in the treatment of bone tumours.

It is clear that the injection of radioactive isotopes may develop into a powerful therapeutic tool. The real value of the applications which have been tried so far has not yet been clearly established. Other applications will undoubtedly be suggested in the next few years, but these are only likely to be effective if they are based on fundamental

knowledge of the distribution of chemicals of various kinds in the body.

The application of isotopes in biology and medicine has been studied in America more than in any other country and the subject is rapidly developing. The intensive physical research which led to the production of atomic bombs has produced cheap isotopes as a by-product. It seems likely that these will be made available to anyone who has got new suggestions about how they might be used and is capable of using them. Many people are anxious to join in these investigations, but not all of them have clear ideas about exactly what they want to do. Enthusiasm is not enough. The really successful investigator is almost always a man who chooses an important problem and then decides on the best way of solving it. It is usually a waste of time to acquire a new research tool and then look round for problems to which it might be applied.

Those who wish to know more about isotopes are advised to consult the paper by Hamilton (1942), or the book by Pollard and Davidson (1942).

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SOME SEROLOGICAL ASPECTS OF INFECTIOUS MONO-NUCLEOSIS WITH SPECIAL REFERENCE TO THE USE OF AGGLUTININ-ABSORPTION TESTS IN DIAGNOSIS *

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THE serological diagnosis of infectious mononucleosis was introduced by Paul and Bunnell (1932), who demonstrated the presence of an agglutinin and hæmolysin for sheep erythrocytes in the serum of cases ; these were found in high concentration during the acute stage of the disease, the amount of hæmagglutinin corresponding to that of hæmolysin, a rather unusual finding, as hæmolysins are usually developed to a much greater extent than hæmagglutinins. The presence of low concentrations of apparently similar antibodies in normal human serum had long been recognised. At first, no qualitative distinction was drawn between these antibodies, but soon a controversy developed concerning their respective natures. A definite qualitative difference between the antibodies present in infectious mononucleosis and in normal human serum can be shown to exist by placing them in contact with various tissue extracts and erythrocytes of different species of animals and observing whether the antibody is bound, or absorbed by these substances ; such absorption tests, as they are called, can be used to differentiate the respective antibodies. In explanation of the use of absorption tests in infectious mononucleosis, reference must be made to the work of Forssman (1911), and the subsequent extension of his findings by other workers.

Forssman discovered that he could produce a powerful hæmolytic antibody for sheep erythrocytes, by the intraperitoneal injection of a watery extract of the organs of the guinea-pig into a rabbit. The term " heterophile " was introduced by Friedemann (1917) and is used to describe Forssman's hæmolysin and so distinguish it from the ordinary sheep cell hæmolysin resulting from the injection of the homologous antigen ; this latter hæmolysin he called " isophile." It should be pointed out that there are other heterophile antibodies than Forssman's, but that the latter may be identified by its affinity for Forssman heterophile antigen. This antigen has been shown to be present in greatest amount in guinea-pig kidney and lung and therefore the former is often used for absorption tests.

Friedemann demonstrated that the hæmolysin for sheep erythrocytes, present in normal human serum, was absorbed by substances known to contain Forssman heterophile antigen, but not by substances lacking

this antigen. He concluded, therefore, that the normal hæmolysin for sheep erythrocytes in human serum was heterophile in nature.

The early workers with rabbit heterophile antiserum failed to demonstrate its agglutinating power. This failure was found by Trou-Hia-Hsu (1922) to be due to the fact that the heterophile agglutinating antibody will only react with sheep erythrocytes which have been allowed to stand for two to three days. When such cells were used, agglutination, which was just as specific as the corresponding hæmolytic reaction, occurred. On this account, directions for the technique of the Paul-Bunnell test usually stressed that the sheep corpuscles should not be used in the fresh state; this, of course, implied that the antibody in infectious mononucleosis behaved in the same manner as the normal heterophile agglutinin.

The assumption, that the hæmolysin and hæmagglutinin in infectious mononucleosis sera were of the Forssman heterophile character, was commonly held until Bailey and Raffel (1935) attempted to absorb the antibodies from 3 cases of the disease, using heterophile absorbing reagents. The antibodies, hæmolysin and hæmagglutinin, resisted this treatment, but were absorbed by either fresh or heated erythrocytes of the ox and sheep. These results showed that the antibodies were neither heterophile nor isophile in character and therefore quite distinct from any of the recognised sheep hæmolysins or hæmagglutinins, including that present in normal human serum.

In the serological diagnosis of infectious mononucleosis by the direct Paul-Bunnell test, the serologist relied upon finding the agglutinin titre for sheep erythrocytes raised above what was considered to be the normal level. Apart from disagreement with regard to what constituted the normal level, the difficulties involved in interpreting this reaction were further manifested when it was appreciated that a certain number of cases received serum therapy, often because the anginal symptoms suggested the possibility of diphtheria or scarlet fever. Consequent upon serum therapy, as demonstrated by Davidsohn (1930-33), a heterophile antibody for sheep erthrocytes is developed ten to twelve days following the injection of horse, or even rabbit (Schiff 1937), serum. Davidsohn noted also that this antibody was present in higher concentrations in cases which developed serum sickness. Taniguchi (1922) suggested that the heterophile antigen present in the horse serum reacted with the normal heterophile antibody in the patient's blood and that this produced the signs of serum sickness. On the other hand, Powell and Jamieson (1935) found the same proportion of cases of serum sickness amongst cases treated with horse serum previously absorbed with heterophile antibody, as with cases given unabsorbed serum. But, whatever relationship this heterophile antibody had to serum disease, the fact remained that it might be present along with the infectious mononucleosis antibody or mistaken for it.

It became imperative to distinguish between these different

antibodies and absorption tests were devised therefore with this aim. Stuart, Fulton, Ash and Gregory (1936) found that the hæmagglutinin produced by the administration of horse serum could be absorbed both by Forssman and non-Forssman antigens, *e.g.* they were absorbed both by guinea-pig kidney and by heated ox cells ; in contrast, the hæmolysin was absorbed only by Forssman antigen. With guinea-pig kidney emulsion and heated ox erthrocytes as absorbing reagents, Stuart, Welch, Cunningham and Burgess (1936) were able to differentiate between normal sheep hæmagglutinin, the hæmagglutinin found after serum administration, and that present in infectious mononucleosis as follows :—

Antibody Present in	Result of Treatment with Guinea-Pig Kidney Suspension.	Result of Treatment with Heated Ox Cell Suspension.
Normal serum	Absorbed	Not absorbed
Serum sickness . . .	Absorbed	Absorbed
Infectious mononucleosis . .	Not absorbed	Absorbed

Davidsohn (1937) described results with a similar technique, and Beer (1936) investigated the absorptive powers of various other erythrocytes. Barrett (1941) used the same reagents as Stuart, but found that the previous methods were not very suitable for tests upon normal sera where the initial titres were so low that it was difficult to decide whether or not absorption had taken place. With a modified technique, he examined 300 normal sera, 31 sera from cases of infectious mononucleosis, and 7 sera from serum therapy cases. This modified technique of Barrett was employed in the work which is now presented.

This investigation into the serological diagnosis of infectious mononucleosis started after Halcrow (1943) had reported an outbreak of the disease at Larbert E.M.S. Hospital. Over the following two years, a careful watch was kept and whenever there was a possibility of this condition, serum was submitted for examination. In most cases, the test was repeated with at least one further specimen. Of the 170 sera analysed in this report, 110 were from Larbert. The remaining 60 cases were patients in Bangour E.M.S. Hospital, and the Edinburgh City, Eastern General and Western General Hospitals. Dr Halcrow and the writer were given full access to the case records and were given any information required concerning the illness ; in this way, the clinical analysis of the cases was made as uniform as possible.

TECHNIQUE

The patient's serum was heated at 56° C. for half an hour to destroy complement, so as to obviate hæmolytic effects.

The Direct Test (Paul-Bunnell).—The following modification was used. Doubling dilutions of the serum ranging from 1/16 were made. To each of these dilutions, an equal volume, 0·5 c.c. of a 1 per cent. suspension of

washed sheep red blood cells, was added. The usual control with saline instead of serum was included. The tubes were shaken and incubated for four hours in a 37° C. incubator (initially two hours in a 37° C. water-bath was employed). The test was placed in the ice-chest overnight and read the next morning. During the course of the investigation, it was found that it was better to make a further reading after placing the test at 37° C. for a period of two hours; in this paper, only the cold temperature titres are recorded. The last tube showing macroscopic agglutination after gently shaking the tube and viewing the contents through a thin layer produced by tilting the tube, was taken as the end-point.

The Absorption Test (Barrett's modification).—The technique described by Barrett (1941) was used throughout this investigation.

RESULTS

1. *The correlation of the ultimate clinical diagnosis with the result of the absorption test.*

Thirty-eight of the patients were ultimately diagnosed to be cases of infectious mononucleosis. The clinical diagnosis of infectious mononucleosis was based upon the occurrence of a characteristic blood picture, accompanied either by fever, glandular enlargement, sore throat, or a combination of these symptoms. In addition to the main clinical feature, which was either fever, glandular enlargement or sore throat, other fairly constant symptoms were noted. These were lassitude and weakness, profuse sweating, headache and inability to concentrate. Secondary infection of the pharynx in the anginous type of case was, in most cases, due to Vincent's infection, but infections with the hæmolytic streptococcus and pneumococcus also occurred. Many cases could be recognised as infectious mononucleosis from clinical and hæmatological investigation alone, provided that the blood picture was typical—W.B.C. 8-20,000 and a mononucleosis of 45-60 per cent. with many abnormal lymphocytes present. These cells of the " glandular fever type " had a cytoplasm which was more basophilic than that of the normal lymphocyte, and, in addition, the cytoplasm was often vacuolated. Their nuclei varied greatly in shape and the chromatin was dense and often fenestrated.

For the purpose of estimating the degree of correlation between the ultimate clinical diagnosis and the result of the absorption test, the cases have been grouped in the following manner :—

	Ultimate Clinical Diagnosis.	Absorption Test.	Number of Cases.
Group I	Typical infectious mononucleosis	+	17
Group II	Typical infectious mononucleosis	—	10
	Typical infectious mononucleosis	±	3
Group III	Atypical infectious mononucleosis	+	8
Group IV	Not infectious mononucleosis	—	132

Group I.—These cases were clinically and hæmatologically typical and, therefore, the agglutinin-absorption reaction, which was positive, in each case, was merely confirmatory. Seventeen cases were of this nature. In two of them, the titre with the direct test was inconclusive (below 1/256) and therefore the absorption test was of value in establishing a definite positive serological result.

Group II.—Cases which were clinically and hæmatologically infectious mononucleosis, but were serologically negative or inconclusive, when examined by the absorption technique. There were 13 cases in this group—34 per cent. of the cases diagnosed as infectious mononucleosis. With 3 of these, a trace of agglutinating antibody was observed after absorption with guinea-pig kidney, but the titre was less than 1/40, and therefore inconclusive. The probable explanation of this was that the serological examination was made late in the course of the illness, in Case 23 during the fifth week, and in the other 2 cases, after six and thirteen weeks respectively. It would be hardly justifiable to include these 3 cases in a sero-negative group ; they were omitted, therefore, in the estimation of the percentage of sero-negative cases. As for the remaining 10 cases, which were serologically negative, 8 were examined during the first three weeks of the illness, that is, during the period in which a positive agglutinin absorption reaction might be most expected. Admittedly, in 5 of these cases only one examination was performed, but in the other 3, the test was repeated. One case was consistently serologically negative, when examined upon the second, twenty-first and twenty-eighth days of illness. These 10 cases form the sero-negative group of cases of infectious mononucleosis and they represent 26 per cent. of the cases diagnosed as infectious mononucleosis.

Group III.—Those cases in which either the blood picture was inconclusive or there were unusual clinical findings rendering the diagnosis difficult. In this group, the absorption test was of considerable importance in establishing the diagnosis of infectious mononucleosis ; short clinical notes will be given to demonstrate this. A fuller account has been given of one case, which was particularly puzzling.

CASE 8.—Admitted with otitis externa of one month's duration, apart from this the only other abnormal clinical findings were enlarged glands in the neck and right axilla. The lymphocytosis was not high (only 32 per cent. of 7000 W.B.C.), but typical " glandular fever cells " were found. The agglutinin-absorption reaction was positive (titre 1/40) this finding was of great value in confirming the hæmatological diagnosis.

CASE 24.—Admitted with a month's history of cough, weakness, sweating and loss of weight. Seven days before admission developed stomatitis. Pyrexia appeared three days after admission. The agglutinin-absorption reaction was positive three days later (titre 1/80). Six days later, the glands in the posterior triangles of the neck were found to be moderately enlarged. At the time of the serological test, the blood picture was as follows : W.B.C.

subacute bacterial endocarditis affecting the aortic cusps and an acute glomerulo-nephritis. No leptospira were found in the tissues stained by Levaditi's method. In the clinician's view, the illness was complicated by a leptospiral jaundice and an attack of infectious mononucleosis. The result of the agglutinin-absorption reaction was evidence in favour of the latter condition being present in the early stages of the illness.

Group IV.—Cases in which infectious mononucleosis was at one time considered owing to certain clinical or hæmatological findings. The agglutinin-absorption reaction was carried out in many cases of infective hepatitis and atypical pneumonia because, as is usual in these conditions, a certain proportion of abnormal lymphocytes were found in the blood ; also included were cases of Vincent's angina, sore throat, tuberculosis, malaria and other febrile illnesses, which were undiagnosed at the time of the serological investigation. In these cases, the serological result was negative and a diagnosis other than infectious mononucleosis was ultimately made. It is conceivable that a certain proportion of this group might have been atypical cases of infectious mononucleosis which were serologically negative, but clinically as well as serologically, the evidence was against such a diagnosis. Included in this group was a case which gave an inconclusive result with the agglutinin-absorption reaction. The following is a brief note upon it :—

CASE 30.—This was a case of chronic tuberculous adenitis, confirmed by biopsy, in a patient who for sixteen months had been treated for pernicious anæmia by intramuscular injections of liver extract. An inconclusive agglutinin-absorption reaction was recorded (titre 1/10). The interest lies in the fact that Bernstein (1940) has recorded a high Paul-Bunnell titre, following parenteral administration of liver extract.

2. *An estimation of the limitations of the direct Paul-Bunnell test,* based upon the results of agglutinin-absorption tests carried out upon all sera showing agglutination with the direct test.

Out of the 170 sera, 91 showed an agglutination titre of 1/32 or over by the direct Paul-Bunnell test. Absorption tests upon these 91 sera showed that those giving a titre of 1/256 or over also gave a positive agglutinin-absorption reaction for infectious mononucleosis, and were clinically typical cases of that disease. Case 23 was an exception to this, for the titre after absorption was reduced to 1/20 (an inconclusive result). Of those giving a titre of 1/128 by the direct test, 6 gave negative absorption tests for infectious mononucleosis. It was evident from the above findings that a titre of less than 1/256 could not be considered as diagnostic of infectious mononucleosis. Table I shows the distribution of the titres recorded in these 91 patients, and the proportion of those which gave a positive agglutinin-absorption reaction for infectious mononucleosis.

It will be seen that 76 patients' sera gave a titre of less than 1/256

(serologically inconclusive), but only 10 of these gave a positive agglutinin-absorption reaction for infectious mononucleosis.

TABLE I

Titre (Direct Test).		Number of Sera.	Number Giving Positive Agglutinin-Absorption Reaction.
Diagnostic 1/256 or over . .		15	14
Inconclusive	1/128 . . .	13	4
	1/64 . . .	33	5
	1/32 . . .	30	1

In comparison, Table II shows how the application of the agglutinin-absorption test reduced the number of inconclusive serological results.

In only 10 cases was an inconclusive result recorded using the agglutinin-absorption test and 3 of these were clinically typical cases

TABLE II

Titre after Absorption with Guinea-Pig Kidney.		Number of Sera.
Positive, i.e. 1/40 or over . .		25
Inconclusive	1/20 . . .	4
	1/10 . . .	6

of infectious mononucleosis; 2 others had received serum therapy and a third (Case 30) had received liver injections, as already mentioned. In all the cases in which the agglutinin-absorption reaction was recorded as positive, the antibody was absorbed by the ox-cell antigen. In 2 of the serum therapy cases (Case 15 and J.F.) the antibody resisted absorption with the ox-cell antigen, and this also happened with one other patient who had no history of serum therapy.

3. *A comparison of the amount of normal Forssman heterophile antibody found in the sera submitted for the Paul-Bunnell test with that found in a series of sera submitted for the routine Wassermann test.*

For this purpose, the 35 sera which contained antibody not absorbed by guinea-pig kidney were excluded. The remaining series of 135 are compared with a series of 120 sera submitted for routine Wassermann tests. This comparison was made because it was noted that the Forssman heterophile antibody titres, which were being recorded for cases in which the diagnosis was ultimately shown to

be other than infectious mononucleosis, were higher than usual, Smeall 1942; it was necessary, therefore, to demonstrate that this was not due to the technique being used. The results are recorded in Table III.

TABLE III

Titre of Forssman Antibody.	Sera Submitted for:			
	Paul-Bunnell Test.		Wassermann Test.	
	Number.	Per cent.	Number.	Per Cent.
1/128	6	4·4	0	...
1/64	25	18·5	5	4·2
1/32	26	18·6	15	12·5
less than 1/32	79	58·5	100	83·3

4. *The results of agglutinin-absorption reactions in cases receiving serum therapy.*

Serum was submitted from 3 cases with a history of recent serum therapy. In Case 15 infectious mononucleosis had been suspected clinically and confirmed serologically before the administration of the serum; three weeks after the injection, the heterophile antibody resisted absorption by *both* guinea-pig kidney and ox cells; prior to the serum therapy, the antibody resisted absorption only by guinea-pig kidney. The serum from one of the other 2 cases (M.T. and J.F.) similarly resisted absorption by both antigens; clinically, these 2 patients were considered to be cases of serum disease. Because of these unexpected results sera were obtained from patients convalescing from diphtheria who had received antitoxic serum; none of these patients had shown signs of serum sickness. The results obtained with these sera are recorded in Table IV.

From Table IV it can be seen that titres of 1/256 and over were reached in serum therapy cases with the direct test, but that in the majority of these cases the titre was considerably reduced by treatment with guinea-pig antigen, and absorption by the ox-cell antigen was not demonstrated. This behaviour distinguished the antibody present from that occurring in the cases of infectious mononucleosis, for, in the latter condition, there was no reduction in titre by treatment with guinea-pig kidney antigen, and the antibody was readily absorbed by the ox-cell antigen. In most of the serum therapy cases, a titre of at least 1/32 was demonstrable and in some (S 2, 16, 12, 14) it appeared to be due to normal heterophile antibody. It would appear that a titre of 1/40 or over after guinea-pig absorption may be expected in cases receiving intravenous or intramuscular horse serum.

TABLE IV

Results of Absorption Tests upon Serum Therapy Cases

| Ref. No. | Antiserum. | | No. of Days since Serum was Given. | Reciprocal of Titre. | | Result of Ox-Cell Absorption. |
	Dose in c.cs.	Route.		Direct Test.	After Treatment with Guinea-Pig Kidney.	
Case 15	70	I.V.I.	21	256	160	Not absorbed
M. T.	10	I.V.I.	10	64	10	I.S.*
J. F.	5	I.M.I.	10	128	20	Not absorbed
S 2	5	I.M.I.	18	64++	I.S.	I.S.
S 16	5	I.M.I.	26	32++	0	...
S 12	8	I.M.I.	28	64	0	...
S 15	8	I.M.I.	34	512	320	Unabsorbed
S 1	5	I.V.I.	24	0	...	...
S 3	5	I.V.I.	13	256	20	Unabsorbed
S 7	5	I.V.I.	23	256	80	Unabsorbed
S 6	5	I.V.I.	26	128++	20	I.S.
S 21	5	I.V.I.	49	128	0	...
S 9	6	I.V.I.	21	512 †	640	Unabsorbed
S 13	6	I.V.I.	34	64	20	Unabsorbed
S 10	6	I.V.I.	36	128	20	I.S.
S 11	20	I.V.I.	18	256	320	Unabsorbed
S 8	20	I.V.I.	21	128	40	Unabsorbed
S 22	20	I.V.I.	32	64	10	I.S.
S 14	20	I.V.I.	36	64++	0	...

* Insufficient Serum to carry out this absorption.

† Highest dilution prepared from that serum.

++ Agglutination disappeared upon warming at 37° C. for 2–4 hours.

5. *Variations in the titre during the course of the illness in cases of infectious mononucleosis.*

The variations in titre of infectious mononucleosis antibody can be followed only by the absorption test, since reactions in low dilutions recorded by the direct test may be due to normal heterophile antibody. This has been done and the results presented in Table V. In some cases, only a single specimen has been taken. It can be seen at a glance that the highest titres are reached about the second or third week and that, as a rule, there is a steady fall so that quite a proportion may be expected to show titres of 1/40 or less after ten or eleven weeks. The second point to note is that definite high-titre and low-titre cases can be recognised. In one low-titre case (C 5), the titre was zero at the sixth week, and in another (C 8) at the third week.

DISCUSSION

In 66 per cent. of the cases of infectious mononucleosis the agglutinin-absorption reaction was positive, in 26 per cent. of the cases it was negative, and in the remaining 8 per cent. of the cases an inconclusive result was recorded. These facts were obtained by

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correlating the ultimate clinical diagnosis with the serological result in each case. In about two-thirds of the cases in which the reaction was positive, the diagnosis could have been made from the clinical and hæmatological findings alone, in the remaining one-third of the cases the results of the agglutinin-absorption reactions were of undoubted value in establishing the diagnosis.

TABLE V

Case.	Reciprocal of Titres after Absorption with Guinea-Pig Kidney Recorded During the 1st, 2nd, 3rd, etc., Weeks of Illness.												
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	16.
C3	2560	1280	640	...	320	...	...	...	...	...	20	0	...
C1	2560	...	2560	2560	...	...	...	...	...	...	...	...	160
C27	...	...	...	...	...	...	...	...	...	...	...	...	1280
C11	...	1280	1280	...	1280	...	...	320	160	160	80	...	...
C6	...	5120	...	...	...	...	...	640	...	...	...	...	...
C12	...	1280	640	320	320	...	...	...	...	...	...	...	...
C19	1280	...	640	...	...	...	...	...	...	40	...	...	...
C2	320	...	320	...	160	...	...	...	20	...	...	...	...
C25	...	...	...	...	...	...	...	...	320	...	...	...	...
C13	...	640	320	160	...	...	...	...	...	...	...	...	...
C17	160	...	640	...	...	...	...	...	...	...	...	...	...
C4	160	80	...	...	...	...	...	...	...	...	...	...	...
C14	...	160	160	...	...	...	...	...	...	...	...	...	...
C15	...	...	80	Given anti-serum	160*	...	...	...	...	...	...	...	...
C5	...	...	80	...	40	0	...	...	...	...	...	...	...
C8	10	40	0	...	...	...	...	...	...	...	...	...	...
C16	...	...	40	...	...	...	...	...	...	...	...	...	...
C20	...	...	...	40	...	...	...	...	...	...	...	...	...
C23	...	...	...	...	20	10	0	...	...	...	...	...	...
C24	...	...	...	...	80	...	...	...	...	...	80	...	...
C26	...	...	...	...	...	...	...	...	...	80	...	...	...

* Not absorbed by ox cells.

One of the main purposes of this investigation was to estimate the limitations of the direct Paul-Bunnell test, and the results obtained by agglutinin-absorption tests have been used to do this. Few will deny that a high-titre Paul-Bunnell reaction (direct test) is significant in the diagnosis of infectious mononucleosis, but with low titres there is difficulty in finding agreement upon the level at which the titre becomes significant. If only a high-titre were accepted, e.g. 1/256, a certain number of cases would be excluded—in this series, 10 out of 25 cases; if, on the other hand, a low titre were accepted, e.g. 1/64, a large number of cases not suffering from infectious mononucleosis would be included—in this series, 30 out of the 170 patients. Even with this low titre, cases might be missed and yet be revealed by the agglutinin-absorption test; moreover, cases of infectious mono-nucleosis in which the normal heterophile antibody has been increased to, or beyond, this low titre would then be falsely classified as serologically positive; this would have occurred in 8 cases if a titre

of 1/64 had been accepted as diagnostic. It should be noted that, of the 25 cases of infectious mononucleosis found positive by the absorption test, only 14 gave a significant titre in the direct Paul-Bunnell test.

We have to differentiate between the heterophile antibody present in infectious mononucleosis, in normal sera, and that which may be present in patients receiving serum therapy. Considering first the normal heterophile antibody it was noticed that a higher average titre was recorded for the sera submitted for the Paul-Bunnell test than for sera requiring routine Wassermann tests, and this was excluding the cases which gave positive agglutinin-absorption reactions and were finally considered to be infectious mononucleosis. The explanation may be two-fold. In the first place, the sera submitted for the Paul-Bunnell test were mostly from patients with *acute febrile* illnesses, whilst those for the Wassermann test were from all kinds of cases, including normal pregnant women. Secondly, there was the age factor; the majority of the cases of suspected infectious mononucleosis were in the twenty to thirty age group. The routine Wassermann cases covered a wider range. G. H. Smith (1937-8) found that, out of 401 sera from people between the ages of one to thirty years, only 4 were completely lacking in heterophile antibody, but, as the age-group rose, the normal titre fell. This might explain why such a high percentage of cases showed titres of 1/32 or 1/64 and it is possible that the normal heterophile antibody is non-specifically increased in all acute febrile illnesses, infectious mononucleosis included. In infectious mononucleosis, of course, we realise that another heterophile antibody may be present. (There was one case recorded here in which the normal heterophile agglutination reached a titre of 1/256 and yet the titre of the " infectious mononucleosis antibody," as demonstrated by the agglutinin-absorption test, was only 1/20.) This means that, before a diagnostic level for the Paul-Bunnell test could be fixed, it would be necessary to find the highest level reached by the normal heterophile antibody in acute febrile illnesses which were clinically not glandular fever. Although not recorded, 15 cases of syphilis in the acute stage were tested (8 with adenitis, 7 with jaundice) and of these 8 gave a titre of 1/32 and 2 (both jaundice cases) gave a titre of 1/128, this was considered to be further evidence of the non-specific stimulation of the normal heterophile antibody in acute febrile illnesses.

The titres recorded for the direct test throughout are low temperature titres (*i.e.* read immediately after removal from the refrigerator). It was noted, as reported by Stuart *et al.* (1934), (1935), that low temperature titres for infectious mononucleosis and " serum sickness " sera were only one tube higher than titres at 37° C. Whereas normal serum titres might show a titre of 1/64 or 1/128 with strong agglutination at refrigerator temperature which disappeared at 37° C. in half to one hour—a drop of at least two to three tubes. On this

account, it is probably better not to refrigerate the direct test, but to make final readings after four hours' incubation at 37° C.

Only a few sera were received from patients who had had serum therapy. With the present technique complete absorption by the antigens was not demonstrated. In Case 15, for example, a positive agglutinin-absorption reaction was demonstrated before the administration of serum but after the injections an antibody was present which resisted absorption by both antigens. Barrett himself only tested seven specimens from patients who had received serum therapy and the titres in these cases before absorption were not much above the normal range; moreover, he stated that "positive absorption tests in patients who may be suffering from serum sickness should: at present be regarded as of doubtful significance."

Many of the sera obtained from convalescent diphtheria patients who had received antitoxin gave similar results. It was noted that absorption with guinea-pig kidney antigen reduced the titre considerably; there was the possibility that this reduction was only apparent, and was due to the absorption of normal Forssman antibody which had been increased in titre by the injection, and was present in greater quantity than the serum sickness antibody. If this had been the case, one would have expected to find a marked fall in the titre of the direct test when it was subsequently warmed to 37° C., and although this was observed in some of the cases, e.g. S 6, it was not in others, e.g. S 3 or S 7. It must be concluded therefore that the serum sickness antibody was partially absorbed by guinea-pig kidney antigen. A similar reaction was reported in one case by Barrett (1941). The writer's experience with Barrett's test would indicate that the heterophile antibody present in serum sickness was incompletely absorbed by both antigens; moreover, it was recognised in this test by the fact that it was only partially absorbed by both antigens. The agglutinin-absorption tests described and used by other workers apparently demonstrated full absorption with both antigens.

Resistance to absorption with guinea-pig kidney antigen was noted in 2 cases with no history of infectious mononucleosis or of serum therapy. In one case (Case 30) the patient was receiving liver injections which are said to give rise to heterophile antibody (Bernstein 1940). In the other case the antibody resisted absorption with both antigens—Barrett reported this in a few cases and, because of it, insisted upon the use of both antigens in the test.

The manner in which the titre altered with the duration of the illness can be seen from Table V; altogether the titres from 21 cases were recorded and the general picture indicated that high titres were reached early in the course of the illness, and that the titre might still be rising during the second and third weeks—the highest titres were reached between the end of the second or third weeks. Following this, the titre gradually subsided and it was possible to find a residual

titre in some cases three or four months after the onset of the illness. Case 27 was exceptional, for a *high* titre was found after fifteen weeks of illness. In some cases a very high titre was recorded (1/2560), in others the titre remained at a much lower level.

" Infectious mononucleosis antibody " behaved like a true antibody, as judged by its variation in titre during the course of the illness, its degree of thermostability and its ability to act at low temperatures. It was noted that the antibody agglutinated fresh erythrocytes to the same titre as erythrocytes which had been kept for one day. The keeping of the erythrocytes for one day is a procedure often recommended in the directions for the Paul-Bunnell test but this is only likely to increase the agglutination effects produced by normal Forssman antibody.

It is hoped that this small series of cases will emphasize the need for applying absorption methods in the routine diagnosis of sera submitted for the Paul-Bunnell test. At least an abridged agglutinin-absorption test with only one antigen should be employed, and the double absorption technique could be reserved for difficult cases, such as those known to have received serum therapy.

SUMMARY

1. The correlation is high between the clinical and the serological diagnosis of infectious mononucleosis when the absorption test is used. (66 per cent.)

2. The direct Paul-Bunnell test is of limited value especially in late and relapsed cases.

3. In high-titre cases (1/256), the direct test will suffice, but a considerable number of cases may never reach such high titre.

4. Definite sero-negative cases occur ; they form a low percentage of this series. (26 per cent.)

5. Variations in titre during the illness have been recorded.

6. An application of Barrett's absorption technique to a series of cases which had received serum therapy did not give satisfactory results, for complete absorption of the antibody, by either of the antigens employed, was not demonstrated.

7. There appears to be a non-specific stimulation of the normal heterophile antibody in acute febrile illnesses.

8. It is suggested that an abridged absorption test should be employed in the routine serological diagnosis of infectious mononucleosis.

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STUDIES ON PHAGOCYTOSIS

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IN his previous paper (1943) the author presented the results of experiments on phagocytosis of *Streptococcus viridans* (Type R). These results and the conclusions drawn from them suggested to the author the desirability of further experiments—first, for comparing whether and how far the results and conclusions described in the earlier paper refer also to other kinds of bacteria.

Some new observations were also made on the phagocytic activity of stored leucocytes and on the peculiar behaviour of the opsonic activity of stored liquid plasma.

EXPERIMENTAL

The bacteria used for the experiments were chosen from those most commonly found in human beings in good health as well as in illness. Two groups of organisms were represented, cocci and bacilli. The cocci belonged to two sub-groups, namely :—

1. " Commensales " sub-group : *Streptococcus fæcalis* and *Staphylococcus albus.*

2. Pathogenic sub-group : *Streptococcus hæmolyticus, Streptococcus viridans, Staphylococcus aureus.*

The group of bacilli was represented by *Bacillus coli* and *Bacillus proteus vulgaris.*

Most of the micro-organisms (*Bacillus coli, Bacillus proteus vulgaris, Staphylococcus aureus, Streptococcus fæcalis*) were obtained by culturing them in human plasma, which had undergone accidental contamination after the filtration of human plasma into bottles.

The remaining kinds of micro-organism were also grown on human plasma, with the exception that previous sterile plasma was deliberately contaminated with the particular species of bacteria, the source of which were pure plated cultures.

The age of the cultures used was within the limits of forty-eight and seventy-two hours.

In one part of the experiments the bacteria used were suspended in the plasma in which they had been cultured. The environment in this case contained the metabolic products of the bacteria present.

By the use of bacteria-suspensions of this kind or alternatively the supernatant fluids of cultures alone, the effects of metabolic products or toxins on the phagocytic power of stored and fresh leucocytes were examined.

The standard method, however, consisted in five-fold washing of bacteria

in physiological saline, so that even traces of used medium with the contained toxins were removed.

The saline suspensions of bacteria without any plasma were not taken up by the leucocytes alone. Spontaneous phagocytosis ceases after the leucocytes had been stored for longer than twenty-four hours. Therefore the phagocytic values obtained with leucocytes stored for more than twenty-four hours are to be considered as the real values. For control purposes suspensions of washed organisms in sterile citrated human plasma were prepared.

All kinds of bacteria suspensions were diluted with saline up to approximately 1000 millions of bacteria per 1 c.c. of suspension, which was sufficient to ensure that even the most active phagocytosis left many bacteria free.

Blood.—All blood was drawn from donors of Group (O), using the apparatus introduced by Stewart (1940). To prevent coagulation the blood was mixed with 3·8 per cent. sodium citrate solution, so that final concentration of this drug in stored blood reached the amount of 0·38 g. per 100 ml.

After thorough mixing in the collecting bottle, part of this blood, with strict aseptic precautions, was distributed for storage into small sterile tubes, so filled and stoppered as to include the minimum of air. The remaining part of the blood was processed into plasma. Both blood tubes and plasma ampoules were stored in a refrigerator at 2° to 5° C.; a fresh tube and ampoules were used daily.

In some experiments fresh leucocytes were required. They were again obtained from the blood of Group (O) donors whose blood (1-2 c.c.) was also arranged to contain 0·38 g. sodium citrate per 100 ml.

Plasma.—For experiments two kinds of plasma were used, stored and fresh. The stored plasma was obtained by centrifuging the blood fresh drawn as mentioned above. The centrifuged plasma was aspirated into 5 c.c. sterile ampoules, which were sealed in a gas flame. Some of those ampoules were placed in a water-bath at 55° to 56° C. for fifteen minutes. Both kinds of plasma—active and inactivated—were stored at 2° to 5° C. The fresh plasma belonged to the blood which was drawn for obtaining fresh leucocytes.

Cytology.—The blood, stored in tubes and used for experiments on consecutive days, was subjected to a morphological examination, namely, total leucocyte count, differential count and the percentage of leucocyte degeneration.

Misshaped nuclei and vacuolated cytoplasm were considered as early signs of degeneration.

Phagocytosis Experiments.—The procedure was to mix equal volumes of the bacterial suspension in physiological saline and the appropriate plasma, and to incubate at 37° C. for thirty minutes with continuous thorough shaking by a machine enclosed in the incubator. After the incubation the phagocytic system was completed by the addition of 1 volume of blood-cell suspension to 2 volumes of the mixture. This was prepared in the case of stored blood by centrifuging, pipetting off the plasma as completely as possible and, without washing, adding 0·5 ml. of normal saline per 2·5 ml. of residual cells.

In some experiments, when testing the effect of the metabolites of certain bacteria on leucocytes, the above-mentioned 0·5 c.c. of saline was replaced by this same amount of the medium in which the organisms had been grown, and this mixture was allowed to stand in room temperature for half an hour, with shaking every five minutes.

The suspension of cells was prepared similarly when fresh blood was used, except that after the initial separation the cells were thrice washed with normal saline.

The complete phagocytic system was incubated for thirty minutes, with continuous shaking. Films were then prepared, dried quickly, and stained with Leishman. The number of ingested bacteria and the number of cells taking part were counted in 200 consecutive polymorphonuclear leucocytes. For the total leucocyte count, the number of cells taking part in phagocytosis, and the average number of ingested bacteria per cell, an index was calculated using the ratio :

Figure observed : Figure obtained after one hour storage.

An " index of degeneration " of stored leucocytes was the number of degenerated forms expressed as a percentage of the total leucocytes.

Results and Discussion

A. *Phagocytic Activity of Stored Leucocytes*

(Fig. 1) Comparing the curves representing the values of phagocytic activity of stored leucocytes on *Bacillus coli*, *Bacillus proteus vulgaris*, *Streptococcus hæmolyticus*, *Streptococcus fæcalis*, *Streptococcus viridans*, *Staphylococcus aureus* and *Staphylococcus albus*, we must notice that they can be divided roughly into three groups. To the first group belong the curves of *B. coli* and *B. proteus*; to the second group those of *Streptococcus fæcalis*, *Streptococcus viridans* and *Staphylococcus albus*. The third group was formed by *Streptococcus hæmolyticus* and *Staphylococcus aureus*. The presented grouping of curves is not based on any fundamental principles, but only on the observed fact that the numerical values fall into three more or less distinct groups. Therefore, no change in the general conclusions should be involved by the joint discussion of those three groups.

(1) *Bacteria washed and suspended in saline with plasma, stored for as many days as the used leucocytes.* Two phases can be roughly distinguished during incubation.
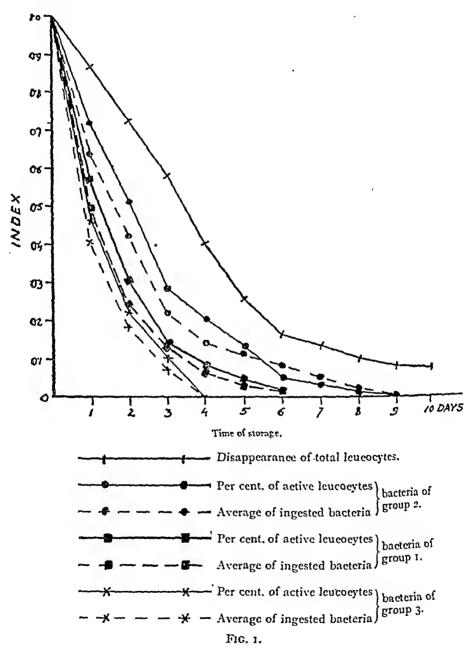
In the first phase the values of the curves are decreasing very rapidly, during the second this decrease is slowed down till finally the values approach zero. The duration of the two phases differs for different bacteria. .

The first phase lasted from forty-eight hours for bacteria of Group 3 up to seventy-two hours for bacteria of Group 2, with Group 1 occupying an intermediate position. The reduction of phagocytic values at the end of this phase amounted in all cases to about 60 to 80 per cent. of the initial values so that the residual activity was 20 to 40 per cent. At the end of the second phase the values reached zero level.

The duration for this second phase depended on the kind of bacteria used. Thus the phagocytosis of *B. coli* or *B. proteus vulgaris* ceased after four days (ninety-six hours) of storage. This refers also

to the third group of bacteria. On the other hand, the phagocytosis of the second group bacteria persisted until the eighth day of storage; the second phase lasted here five days.

The phagocytic power of the same stored leucocytes for bacteria

Time of storage.

———+———————+——— Disappearance of total leucocytes.

———o———————●——— Per cent. of active leucocytes ⎫ bacteria of
— -o- — — — -●- — Average of ingested bacteria ⎭ group 2.

———▇———————▇——— Per cent. of active leucocytes ⎫ bacteria of
— -▇- — — — -▇- — Average of ingested bacteria ⎭ group 1.

———×———————×——— Per cent. of active leucocytes ⎫ bacteria of
— -×- — — — -✳- — Average of ingested bacteria ⎭ group 3.

Fig. 1.

opsonised by fresh plasma, shows an increase of the average number of organisms ingested per cell as well as of the percentage of leucocytes taking part. It shows that fresh plasma possesses a greater opsonising power than stored plasma. Fresh plasma gives higher phagocytic figures with all organisms than does stored plasma. Moreover, fresh plasma prolongs the activity of stored leucocytes approximately

doubling the period of activity against bacteria of Groups 1 and 2, but giving only 50 per cent. increase against bacteria of Group 3.

(2) *Phagocytosis by stored leucocytes of bacteria not washed with saline but suspended in the medium on which grown.*

The phagocytic values for bacteria belonging to Groups 1 and 2 when treated in this way were nearly identical with the curves for these same bacteria washed and suspended in saline. Slight decreases observed were just within the limits of biological error.

Interesting observations were yielded by use of bacteria of Group 3 (*Streptococcus hæmolyticus* and *Staphylococcus aureus*) suspended in the medium on which they were previously grown. Using stored leucocytes and stored plasma the phagocytosis of *Streptococcus hæmolyticus* or *Staphylococcus aureus* suspended in saline ceases about the fourth day of storage. However, if the bacteria suspension is made in the medium in which they were grown, phagocytosis definitely disappears before the second day of storage. (With other kinds of bacteria those differences were not observed.) The substitution of fresh for stored plasma causes no increase in phagocytic figures nor does it lengthen the period of phagocytic activity. Analysis of the behaviour of phagocytosis in the case of both fresh and stored plasma leads us to the conclusion that the plasma's opsonising power does not play the most important rôle, but that another factor is interfering in the phagocytic phenomenon. The existence of this factor is made clearer by more detailed consideration of the experimental findings.
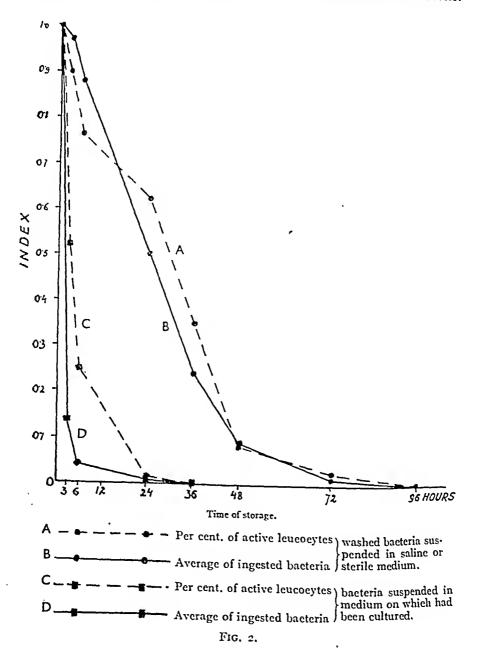
Using for the phagocytic system bacteria of Group 3 (*Streptococcus hæmolyticus* and *Staphylococcus aureus*) suspended in the medium in which they were grown, one sees that curves representing an average number of organisms ingested per cell and the percentage of active stored leucocytes, both fall rapidly (Fig. 2). Even after three hours' storage the percentage of active leucocytes in this case is only half that found when these same leucocytes were used, but with bacteria washed and suspended in saline or in sterile medium, the average of ingested organisms decreases nearly to 1/7 (Curves *c* and *d*). In the blood stored for six hours the number of active phagocytic cells is about 13·5 per cent. of the active leucocytes at the starting-point, and the average of ingested bacteria drops nearly twenty-five times.

By comparison with the corresponding curves for washed bacteria (Curves *a* and *b*), one sees that these phagocytic values after six hours' storage of leucocytes, and the use of unwashed organisms are as low as those obtained with the same leucocytes; but with bacteria washed and suspended in saline or in sterile medium—as regards percentage of active cells after thirty-six hours, and average as regards number of ingested bacteria after seventy-two hours.

Briefly, after only six hours' storage, the phagocytosis falls to a very low level. The values after twenty-four hours are hardly detectable, and after thirty-six hours of storage phagocytosis in this case ceases altogether.

This phenomenon has also been observed when stored whole blood is employed.

Fig. 2 was made using *Streptococcus hæmolyticus*, but curves for *Staphylococcus aureus* in general lead to the same conclusions. It

A — •—•—•—•— Per cent. of active leucocytes ⎫ washed bacteria sus-
B —————○———— Average of ingested bacteria ⎬ pended in saline or
                                                              ⎭ sterile medium.

C —■——■— Per cent. of active leucocytes ⎫ bacteria suspended in
D —————■———— Average of ingested bacteria ⎬ medium on which had
                                                              ⎭ been cultured.

FIG. 2.

is obviously desirable to try to find the meaning of the phenomenon shown in this figure and described above.

The elements common to these phagocytic systems were leucocytes, plasma and bacteria ; but the only different one was the environment in which bacteria were suspended. It is evident that this suspending medium must contain the agent responsible for the differences noticed.

In it the active part might be the medium itself or toxins and metabolic products of the bacteria, or both. In order to decide this, some of the washed bacteria were suspended in sterile culture-medium (citrated plasma and glucose) and some in supernatant fluid, *i.e.* the fluid obtained by centrifuging over bacteria growing on this medium. In the experiment with bacteria suspended in sterile culture-medium, the phagocytic values obtained were on the same level as figures obtained with bacteria suspended in saline. When supernatant fluid from the growth was used as suspending medium, the values obtained were as before, lower than those obtained in control systems. In other words, the supernatant fluid of the bacteria-growth, but not the medium itself, possessed the inhibitory effect on phagocytosis. This means that the medium undergoes some change which is responsible for its inhibitory effect on phagocytosis.

The lowering of phagocytic figures in this case may be caused by the effect of this changed medium on bacteria, in some manner perhaps rendering difficult effective opsonisation or on the leucocytes themselves. The separate incubation of bacteria and leucocytes with the supernatant growth-medium fluid demonstrates that the sensitive point is the leucocytic cell and not the bacteria.

Analysing the mentioned phagocytic curves we must notice the fact that under the influence of supernatant fluid, not only the average of ingestion decreases but also, and that is important, the number of active leucocytes. The number of degenerated leucocytes after six hours' storage is practically zero, and the first conspicuous degenerative changes are hardly to be seen after twenty-four hours' storage (see previous (1943) paper, Fig. 1, Curve F_1). Looking carefully at the course of phagocytic curves in this particular case, we see that during six hours period of storage, when bacteria are suspended in saline or in sterile growth-medium, the number of active leucocytes decreases about 23 per cent. and the average number of ingested organisms about 12 per cent. of the initial values. But when bacteria suspended in their medium were used the number of active leucocytes after six hours' storage decreases about sevenfold, and the remaining phagocytic cells retain only $3\frac{1}{2}$ per cent. of an initial ingestive power (Fig. 2, Curves c and d).

The conclusion is that storage causes such changes in the leucocytes, that the influence of factors (leucocidins, van der Velde 1894) produced in supernatant fluid from growth of certain bacteria paralyses the phagocytic activity of the leucocytes. The sensitivity of the leucocytes to this inhibitory effect increases almost with every minute of storage, and specially during the first three to six hours.

It is evident that even during the very early period of storage the leucocytes suffer changes which, though unobserved under the microscope, can be detected by the paralysing effect of these supernatant fluids. These changes can be detected even at the first hour of storage.

B. *Phagocytic Activity of Fresh Leucocytes*

The curves representing phagocytic values obtained in systems containing fresh leucocytes and stored plasma follow roughly the curves of the previous paper (1943, Fig. 2), and show that stored plasma maintains far longer the ability of opsonising all the bacteria used for ingestion by fresh leucocytes, than for ingestion by stored leucocytes.

The Influence of Supernatant Fluid from the Growth of Streptococcus hæmolyticus *and* Staphylococcus aureus *on the Fresh Leucocytes.*—The incubation of fresh leucocytes with either kind of bacteria in the unwashed state, or washed and suspended in supernatant fluid causes weakening of their phagocytic activity with regard to the average of ingestion as well as to the percentage of cells participating in action (*vide* Table).

TABLE

Fresh Leucocytes.			
Bacteria Washed.		Bacteria Unwashed.	
Per Cent. of Active Cells	Average of Ingested Bacteria.	Per Cent. of Active Cells.	Average of Ingested Bacteria.
37	10·3	32	8·9
46	8·1	40	6·0
28	6·4	27	5·1
32	7·3	31	5·7

Staphylococcus aureus.

The decrease of these values is not very great and equals 3 to 10 per cent. of active leucocytes and 1 to 14 per cent. average of ingestion, and this is much less than the lowering obtained by the use of unwashed bacteria and leucocytes stored for three hours. This phenomenon brings us to the conclusion that among active fresh leucocytes the toxins contained in the supernatant fluid eliminate chiefly the weaker elements. The remaining leucocytes, on the other hand, are subjected to insignificant damage, which is expressed in a very small decrease of the average of ingestion by the remaining active leucocytes.

INACTIVATION AND REACTIVATION OF STORED PLASMA

As has been pointed out in the description of methods, the blood-plasma, after separating the cells by centrifuging and aspirating, was divided into two parts. One part was distributed into sterile ampoules, which were then sealed. The procedure with another part of plasma was identical, with the exception that before distribution the plasma was subjected to " inactivation " by heating for fifteen minutes at 55° to 56° C.

For all the experiments three species of bacteria were used :

Staphylococcus albus, Bacillus coli and *Streptococcus fæcalis.* The results were essentially the same for all.

A. *Phagocytosis in Systems containing Stored Leucocytes*

Analysing the curves of opsonising activity of both kinds of plasma for *Staphylococcus albus* (*Bacillus coli* and *Streptococcus*

Time of storage.

A ————•————————•———— Per cent. of active leucocytes ⎫
B —•— — — —•— — Average of ingested bacteria ⎬ with unheated plasma.

C ————■————————■———— Per cent. of active leucocytes ⎫
D —■— — — —■— — Average of ingested bacteria ⎬ with heated plasma.

E —✕— — — ✱— — Average of ingested bacteria after addition of fresh plasma.

FIG. 3.
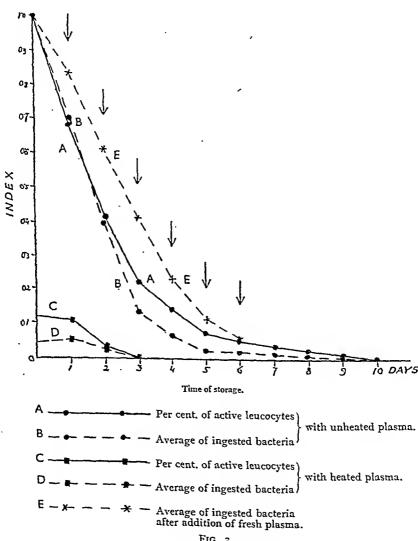
fæcalis behaved similarly), one sees that the curves for unheated plasma (Fig. 3, *a* and *b*) coincide with the curves of phagocytic activity published in 1943. But the opsonising power by heated plasma of bacteria to be ingested by stored leucocytes disappears after forty-eight hours' storage (Fig. 3, Curves *c* and *d*).

In discussing Fig. 3 we must notice that from the very beginning of storage the opsonising power of heated plasma is negligible. In the phagocytic systems containing stored blood and heated stored plasma (Curves *c* and *d*) the percentage of active leucocytes and average number of bacteria ingested per leucocyte at the beginning of storage are only about 20 per cent. of the initial values which are obtained in systems containing unheated stored plasma. These values obtained with heated plasma fluctuate roughly about this same level and disappear on the third day of storage.
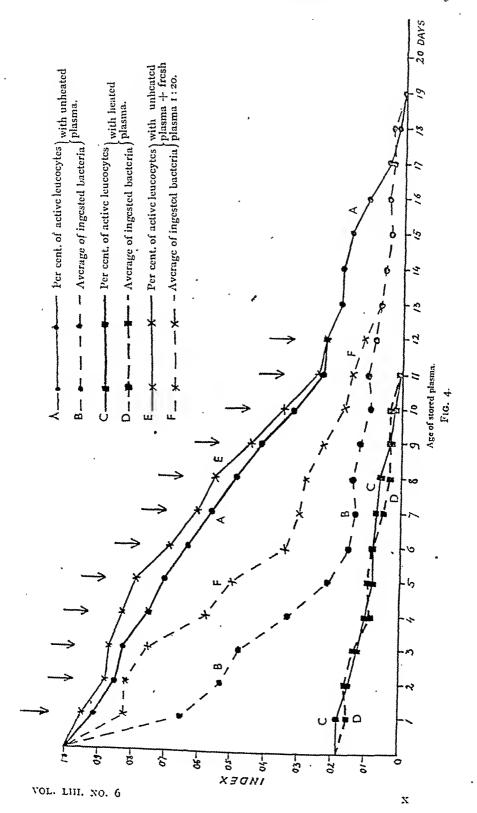
B. *Phagocytosis in Systems containing Fresh Leucocytes*

In the systems containing bacteria opsonised with unheated plasma the curves representing phagocytic values for the same strain of *Staphylococcus albus*, as used in the previous experiment, are shown in Fig. 4 (Curves *a* and *b*). The opsonising power of unheated plasma lasts, in this case, until about the nineteenth day of storage; moreover, during the first five days of storage, the number of active leucocytes falls about 30 per cent., and the average number of bacteria ingested per cell falls to about 20 per cent. of initial values respectively. The application of heated stored plasma causes a decrease both of active leucocytes and of the average number of bacteria ingested to 18 per cent. of the initial values obtained with unheated plasma (Fig. 4, Curves *c* and *d*). The phagocytosis of bacteria opsonised by heated stored plasma ceases about the tenth day of storage.

Reactivation of Opsonising Power.—The addition of a small amount of fresh plasma (1 : 20) to the unheated stored plasma causes an increase of opsonising power of the stored plasma. This can be observed very soon, almost in the first days of storage (*vide* Fig. 3, Curve *e*; and Fig. 4, Curves *e* and *f*). This intensifying action of small amounts of fresh plasma is well known to us from the author's previous paper which suggested also an explanation of this regenerative action of fresh plasma.

However, the author has been unable to demonstrate any regenerative action of fresh plasma on the opsonising activity of stored plasma inactivated by heat. The slight increase of phagocytosis after the addition of fresh plasma to the heated stored plasma equals merely the arithmetical sum of the opsonising power of heated stored plasma and the added fresh plasma; but sometimes, though very rarely, quite high figures were obtained, which were much higher than the arithmetical sum. The reason for the occurrence of these scattered cases is impossible to explain now. From the control point of view the opsonising power of fresh plasma diluted in physiological saline in relation to 1 : 20 cannot be considered as the effect of only plasma traces, because the results of roughly this same level are obtained with the saline alone.

Consideration of both series of experiments and their results (Figs. 3 and 4) suggests the conclusion that the whole opsonising power

Per cent. of active leucocytes} with unheated
Average of ingested bacteria} plasma.

Per cent. of active leucocytes} with heated
Average of ingested bacteria} plasma.

Per cent. of active leucocytes} with unheated
Average of ingested bacteria} plasma + fresh plasma 1 : 20.

A ——•——
B ——•——
C ——■——
D ——■——
E ——×——
F ——×——

Age of stored plasma.

FIG. 4.

INDEX

20 DAYS

of the normal blood consists of two parts, one of which is roughly five times greater than the other as regards the percentage of active leucocytes.

This greater part is sensitive to inactivation by heat or perhaps storage. The inactivation by heat is quick, rapid, but slow by storage (seventeen to nineteen days).

The smaller part (about 1/5) of the total opsonising power is thermo-stable and resistant to storage over a certain period of time. This smaller part, I suppose, is identical with the " residual phagocytic factor " of Ward and Enders (1933).

In both kinds of stored plasma, heated and unheated, the value of this " residual phagocytic factor " is nearly the same and equals as much as the phagocytosis of heated plasma.

After the addition of fresh plasma in the proportion of. 1 : 20 the interesting phenomenon takes place, that although the opsonising power of stored unheated plasma increases quite considerably (in first days of storage the increase is about 20 per cent.), the addition of these small amounts of fresh plasma has no detectable effect on the " residual phagocytic factor " in stored heated plasma. From this it is possible to suppose that certain irreversible changes occur in heated plasma. The character of these changes is unknown, but the manifestation of one of them is the lack of reaction of heated stored plasma to the stimulating action of small amounts of fresh plasma. According to the results presented, the author was unable to confirm fully the conclusions of certain other writers (Cowie and Chapin, 1907 ; Dean, 1907 ; Ward and Enders, 1933).

The so-called " residual phagocytic factor " appears to cause the " basic " opsonisation, which is roughly of the same strength for different kinds of bacteria. No doubt it is some fraction of the protein complex, which possesses the opsonising power for different bacteria, but it has not any specific activity.

During the course of active immunisation, natural or artificial, the serum increases its opsonising power for the organism used as antigen, but it does not change its capacities for other kinds of bacteria, except those very closely related to the bacterium which served as antigen. But the immunisation does not increase the opsonising power of the " residual phagocytic factor " (Ward and Enders, 1933).

The important point in this is that the organisms " opsonised " by this " residual phagocytic factor " can be phagocyted only and merely by the relatively fresh and little degenerated leucocytes. The leucocyte stored for seventy-two hours has lost the property of phagocyting the organisms opsonised by the " residual factor."

The observations presented give evidence that the " residual phagocytic factor " does not cause complete " coating "—opsonisation —of the organisms, because with the leucocytes stored for seventy-two hours phagocytosis could not take place ; only the stronger fresh leucocytes are able to phagocyte those " partially-prepared " bacteria.

The admixture of fresh blood-plasma introduces a factor which increases the potentiation of the opsonising phenomenon as a result of which the average number of engulfed bacteria increases, but the percentage of participating leucocytes does not undergo any change. It means that only the "stronger" leucocytes are able always to phagocyte because of "imperfectly" opsonised bacteria.

Consideration of the results presented supports the conclusions drawn by the author in 1943, that: (1) during opsonisation the bacteria combine in some possible loose chemical way with opsonins, and the resulting compound may be pictured as BO_x, the organism being capable of combining with one or more opsonin molecules. It is possible that x is variable, *i.e.* that there are degrees of opsonisation, and that the more nearly x approaches the maximum possible, the greater the tendency of BO_x to be phagocyted.

(2) The formation of BO_x is activated or potentiated by a second factor, possibly complement or one of its components.

(3) Phagocytosis of the opsonised organism requires a "normal" leucocyte and may be pictured as involving chemical action between the compound BO_x and active groups at the cell surface. Changes in the cell during storage must involve alterations of the cell surface which prevent this action from occurring.

GENERAL CONCLUSIONS

1. It has been shown that the conclusions reached in the author's previous paper (1943) about the phagocytic phenomenon with stored leucocytes and the opsonic power of stored blood-plasma for *Streptococcus viridans* can be extended also for other bacteria—*Bacillus coli, Bacillus proteus vulgaris, Streptococcus fæcalis, Streptococcus viridans, Streptococcus hæmolyticus, Staphylococcus aureus* and *Staphylococcus albus.*

2. The medium in which *Streptococcus hæmolyticus* and *Staphylococcus aureus* were grown contains a factor which possesses an inhibitory influence on the phagocytic activity of leucocytes, eliminating the weaker cells and decreasing the average number of engulfed bacteria.

3. Fresh leucocytes react very little on this inhibitory influence of supernatant fluid from media.

4. Contrary to the previous conclusions (1943) the leucocytes stored even for a relatively short time gave evidence that even the shortest time of storage causes such degenerative changes in the phagocytic cell that certain toxins (leucocidines ?) can freely exercise their inhibitory influence.

5. The tendency of leucocytes for spontaneous phagocytosis ceases to appear during the first twenty-four hours of storage, so that the results obtained after that time should be considered as the real values.

6. In the process of opsonisation two kinds of opsonins are par-

ticipating.   One is formed by the thermostable "residual phagocytic factor" (Ward and Enders, 1933), and the second, almost five times stronger, but needing for its activity a factor which is inactivated both by heat and by storage of plasma.

7. The minimum of opsonisation—BO (minimum)—is caused by this weaker thermostable opsonising factor, the "residual phagocytic factor."

8. The opsonising activity of plasma inactivated by storage undergoes regeneration within certain limits by the influence of the small amounts of fresh plasma.

9. The "residual phagocytic factor" causes the "basic" opsonisation of various species of bacteria, and thus possesses no selective activity.

10. The changes which take place in plasma during its inactivation by heat are irreversible, in consequence of which the addition of small amounts of fresh plasma does not regenerate the lost opsonic activity.

11. Misshaped nuclei and vacuolated cytoplasm are regarded as early signs of degeneration.

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DANIEL WHISTLER AND HIS CONTRIBUTION TO PÆDIATRICS

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ON 18th October 1645 there was read at Leyden the Latin thesis of young Daniel Whistler for the degree of Doctor of Physic. The importance of this thesis lies in the fact that it contained the first complete clinical account of rickets, and preceded by five years the monumental and authoritative work of Francis Glisson and his colleagues.

Prior to Whistler's description there had been no clear account of rickets. That the disease was not unknown to the ancients is shown by the allusions to it in the writings of Soranus of Ephesus (second century A.D.), and in Galen's *De morborum causis* (Findlay, 1934). Foote (1927), from a study of the later fifteenth and sixteenth century paintings by Netherlands and German masters, demonstrated the existence of rickety deformities in these times. Hieronymus Reusner published at Basle in 1582 a description of a disease confined to children and characterised by weakness of the limbs, chest deformities and bow legs. This disease, obviously a brief description of rickets, Reusner stated was common in Switzerland and Holland. With the earlier writers, however, there appears to have been no very clear-cut conception of rickets, and it was doubtless confounded with other diseases affecting the skeleton in children (Still, 1931). Yet it is remarkable that no adequate description of rickets was published before 1645.

The word *rickets* was apparently first used in England about 1625, and it appeared as the cause of fourteen deaths in a Bill of Mortality dated 1634, while the word *rickety* was not in use until 1738 (Brown, 1942).

A.—WHISTLER'S DESCRIPTION OF RICKETS

Whistler's book was published a short time after the reading of his thesis in 1645. It was a small quarto volume of some eighteen pages, though when it was reprinted in 1684, it was in octavo. Copies of the 1645 edition are very rare, but there is a copy in the Library of the Royal College of Physicians of London and another in the British Museum.

The title-page bears the heading : " De morbo puerili Anglorum quem patrio idiomate indigenae vocant *The Rickets* . . . discutiendam proponit Daniel Whistler, Anglo-Saxonicus-Orientalis," and shows

that the disputation was held at Leyden by authority of the Rector, the Reverend Dr John Polyander à Kerchoven, for the Degree of Doctor of Physic.

Near the bottom of the title-page is a woodcut of a bird which Moore (1884) considered to be a representation of an ostrich holding a horseshoe in its beak. Moore also suggests that the bird's supposed ability to digest iron appealed to Dutch booksellers so that they thought it "an appropriate symbol of the capacity for assimilating knowledge in its toughest form." Below this symbol is the place, Leyden, the name of the publisher, Wilhem Christian Boxius, and the date of publication, 1645. The reprint of 1684, published just prior to Whistler's death, omits the woodcut of the bird.

The reverse side of the title-page bears the dedication to two members of the Whistler family.

Fourteen pages are devoted to the essay, which is divided into seventeen sections. The following is a brief summary of the text in modernised terminology :

In Section I, note is made of the fact that the disease is common in England. Section II informs us that the ancients knew the symptoms of rickets but as disconnected phenomena and not, as Whistler says, " The syndrome of signs making in conjunction one pathognomonic whole " (Still's translation). He also observes that for the previous twenty-six years, " more or less," the disease had been known and that the name " rickets " may have been derived from the name of some quack who first treated the disease, or that it was a corruption of the Dorsetshire word " to rucket " or breathe with difficulty. Whistler himself proposes the name " Paedosplanchnosteocaces," which fortunately never came into use.

The seventeen cardinal symptoms and signs of rickets described by Whistler occupy the next section. These are :—(*a*) abdominal distension ; (*b*) enlarged epiphyses, especially those of the arms and feet ; (*c*) rickety rosary ; (*d*) general muscular hypotonia ; limb deformities ; lumbar kyphosis, later followed by an inability to sit up if the disease is progressing ; (*e*) large head, often with hydrocephalus ; (*f*) flabbiness of the soft parts and abnormal flexibility of the joints ; (*g*) delayed dentition which is often troublesome, with early decay of the erupted teeth ; (*h*) narrowness of the chest, pigeon breast or depressed sternum ; (*i*) increasing dyspnœa, often with cough ; (*j*) slow fever ; (*k*) feeble and irregular pulse ; (*l*) urine changes ; (*m*) often diarrhœa and vomiting ; (*n*) variable appetite ; (*o*) normal sleep, " unless something prevents " it ; (*p*) philosopher's mien, though those with large heads are dull ; (*q*) pustules and blotches of the face, chest and limbs.

In subsequent sections, Whistler describes, very inadequately and without first-hand knowledge, the post-mortem appearances in rickets, and speculates on the pathology of the disease. He is of the opinion

that rickets is due to the clot-forming part of the blood becoming impacted in the viscera, while the serous portion is set free in the whole body, causing the various swellings of the abdomen, epiphyses and head, and contributing to the general flabbiness of the tissues.

A full definition of the disease in eight lines, all in italics, and a reiteration of the main points of pathology occupy Section XI.

Sections XII to XV are taken up by a discussion of the causes of some of the major symptoms and signs.

Prognosis is epitomised in Section XVI, under the following heads :—(a) All die who are affected at or before birth ; (b) females recover quicker than males ; (c) those with hydrocephalus succumb ; (d) those who bear movement of the body best recover easiest ; (e) those whose feet are attacked are easily cured, as are those who are attacked at a more advanced age ; (f) those who can scarcely hold up their heads and those who have much dyspnœa rarely recover ; with suppuration of the lungs, never ; (g) a small, unequal and rapid pulse, especially a weak one, is a bad sign.

The last section, occupying two and a half pages of text, deals with treatment, and Whistler recommends drugs of a wide variety.

The summary of the contents of Whistler's book as given above has been mainly derived from Moore (1884).

B.—DANIEL WHISTLER—THE MAN

Daniel Whistler, one of three sons of William Whistler, was born at Walthamstow, Essex, in 1620. Receiving his early education at the Free School at Thame, Oxfordshire, he entered Merton College, Oxford, in January 1639, and graduated B.A. in 1642. On 8th August of the same year he began the study of medicine at Leyden, and graduated there on 19th October 1645, having in the meantime returned to Oxford for a short time to take his M.A. on 8th February 1644.

Returning to England, Whistler was incorporated M.D. at Oxford on 20th May 1647, and on 13th June 1648 was elected Professor of Geometry at Gresham College, and at the same time was appointed Linacre reader at Oxford. He resigned his professorship on his marriage in 1656. The Royal College of Physicians of London elected him a Fellow in 1649.

Whistler had some experience of naval surgery in 1652 when he took charge of wounded seamen, while in October 1653, he accompanied Bulstrode Whitelocke in the latter's embassy to Sweden. In this post he appears more the diplomat and politician than the physician, and his merits as such were evidently appreciated by Oliver Cromwell with whom Whistler corresponded.

Back home in London by July 1654, Whistler resumed his practice, and soon became an active Fellow of the Royal College of Physicians. He was Harveian Orator in 1659 ; Censor twelve times between

1657 and 1680, and was one of the Censors in 1663 when Sydenham was admitted a Licentiate of the College (Latham, 1648); Registrar in 1674-1682; Treasurer in 1682, and finally succeeded Dr Thomas Coxe as President in 1683. This position he held till his death on 11th May 1684. Dr Coxe, whom he succeeded as President of the College, was the same Dr Coxe who persuaded Sydenham to take up the study of medicine, and who was deprived of his presidential chair because he was " whiggishly inclined."

Whistler was a man of considerable versatility as his medical, mathematical, political and social activities indicate. He was a man of culture and wit, and his variety of scientific interests obtained for him election as Fellow of the Royal Society in 1663. He spoke French and Latin well, and could turn out creditable Latin verse when the situation called for such.

Socially, Whistler enjoyed wide popularity and was a good mixer. Even as a student he apparently had the time to devote to social activities, for he was the recipient of a volume of Latin verse compiled by his fellow-classmates on the occasion of his graduation. In London, he was a frequenter of taverns, especially the Crown Tavern. He was well known to the two eminent diarists of the period. Evelyn supped often with Whistler and other eminent figures of the time, as he records in his diary on 29th February 1675-76, and 29th January 1682-83. On 20th March 1682-83, Evelyn " Dined at Dr. Whistler's, at the Physicians' College, with Sir Thomas Millington, both learned men ; Dr W. the most facetious man in nature, and now Censor of the College . . ." Pepys speaks of Whistler frequently, mentioning that he had two daughters " very pretty and mirthfull." On 4th February 1660, Pepys makes this entry : " We sat late, talking with my Lady and others, and Dr Whistler, who I found good company and a very ingenious man : so home and to bed." Pepys dined with Whistler and others " of the most eminent worth," on 15th February 1664, while on 16th November 1666, in a discussion with Robert Hooke on blood transfusion experiments in dogs, he " doubts not its being found of great use to men ; and so do Dr Whistler who dined with us at the tavern."

Whistler's love of tavern life, and possibly his " very pretty and mirthfull " daughters seem to have cost him dear in time and money, for Munk (1878) quotes Wood as saying " he married a rich widow and his practice for many years before his death brought him £1000 per annum, yet he died very much in debt, and worse than nothing." As Registrar of the College of Physicians, Whistler was careless in the discharge of his duties, and in spite of the trust reposed in him by his colleagues and his elevation to yet higher offices, he got deeper into debt by reason of his negligence of financial matters involving the College, which, some maintain, amounted to embezzlement. This unfortunate side of Whistler's life has undoubtedly coloured many of the accounts of his life and work and tended to obscure the merits he

possessed. Still (1931) brings forward evidence, in the form of his will made the day before he died, to show that Whistler, for all his carelessness in matters affecting the welfare of the College, displayed an affection for and interest in the College which seem foreign to an embezzler's nature. As an example of this seeming interest in its good, Whistler directs that the College be given " all his books, manuscripts and rareyties in the shelves and drawers which are in my closett . . . " His friend, and one of the executors of his estate, Sir John Cutler, made good, by loans, the losses which the College had sustained through Whistler's indifference to financial affairs.

C.—WHISTLER'S CLAIM TO WIDER RECOGNITION

Rarely is it given to young men of twenty-five years of age to write an original account of a disease, but it is generally conceded that Whistler gave the first complete clinical account of rickets. Opinions are divided, however, as to whether his description was original or was compiled as a result of what he had heard of the work of Glisson and his colleagues. Allusion was made by Whistler in his work to a distinguished physician whom many suppose to have been Glisson. While it is difficult to imagine how young Whistler could describe as well as he did the *morbus Anglorum* when he had resided in Leyden for the three years previous to the reading of his thesis, it should be remembered that he had lived as a youngster near London, and we know that rickets of a fairly severe form was common there. Whistler would thus have had ample opportunity of visualising the crippling effects of the disease. Mayhap cases of the same disease that he saw in Holland brought back to his memory the deformed little Londoners, and owing to the current lack of interest by both English and Dutch physicians to these rickety cases, he resolved to draw the attention of the profession to rickets by affording as full a description of the disease as he could give.

It is possible that Whistler, during his short sojourn in England in 1644, when he returned to Oxford to take his M.A. degree, may have heard whisperings or even open discussion on Glisson's work. In this connection, Glisson informs us in his book that for the five years prior to its publication, a small group of medical men had met regularly in London to discuss scientific subjects, including rickets, " and when thes things had opened a way in some sort to the deeper enquiry and search after the condition and cure of this Diseas ; we thought it might prove a very successful undertaking to recal those Papers once again to a Review ; and . . . to prepare a Tractate of this Diseas." Drummond and Wilbraham (1939) draw attention to the similarity in the title-pages of both Whistler's and Glisson's accounts and point out the unlikelihood of Glisson and his colleagues having chosen a title for their work five years in advance of its publication. Glisson never mentions Whistler nor alludes to any previous description

of rickets, though Arnold Boot had published an account of it in 1649 in London.

The weakest part in Whistler's essay is the absence of a first-hand account of the morbid anatomy of rickets, which was so laboriously given by Glisson. As a *clinical* description of rickets, however, Whistler's work deserves the recognition which is so clearly his due. It is inconceivable that so concise and yet so complete a description of the disease could be compiled merely from hearsay. It must have been done as the result of careful personal observation by an astute though indolent man.

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DOUGLAS CHALMERS WATSON

OBITUARY

DOUGLAS CHALMERS WATSON
M.D., F.R.C.P.Ed.

CHALMERS WATSON died suddenly on 7th April 1946 at Fenton Barns in his seventy-sixth year; and his passing has removed a striking and distinguished personality from Edinburgh Medicine.

His heredity and early environment (both subjects of particular interest to him) played an important rôle in his ultimate life and outlook. His father was a much respected practitioner at Mid-Calder, his mother a member of a well-known Lothian agricultural family; and together they created an atmosphere in the home which served to kindle in him an early enthusiasm for both medicine and agriculture. With these broad interests in his early life he developed a sense of perspective which enabled him to place the art and science of medicine in its correct relation to the whole range of biology. This width of outlook and catholicity of interest were indeed striking characteristics of the man.

He was educated at the village school at Mid-Calder, George Watson's College and Edinburgh University, where he gained the Wightman Prize in Clinical Medicine on graduation in 1892.

As house physician to Sir Thomas Fraser at the Royal Infirmary, and to Dr Burn Murdoch and Mr Joseph Bell at the Royal Hospital for Sick Children, and as Clinical Assistant to such distinguished pioneers as Argyll-Robertson and his colleagues in the various special departments in the Edinburgh School of half a century ago, he laid the foundation of a wide knowledge and a scientific approach to medicine and to life. Recognition of his outstanding ability came early when he was appointed editor of the *Encyclopædia Medica* only eight years after graduation.

His originality of thought and enquiring dynamic mind soon created an impulse towards research—a purpose which he pursued with undiminished enthusiasm until the last days of his life. It is interesting to recall that his earliest investigations were in the province of organotherapy, and in 1900 he submitted an M.D. thesis on the value of bone marrow extract in the treatment of certain chronic skin diseases. At the beginning of the century he commenced his life-long study of the problems of nutrition in the laboratories of Sir E. A. Sharpey-Schafer. His initial investigations were concerned with the variations in health of laboratory animals, and the influence of various diets on tissue histology. The outstanding nature of this work was acknowledged by the award by the College of Physicians of Philadelphia of the Alvarenga Prize—a prize, open to world-wide competition, for an essay on scientific work in relation to clinical medicine. Chalmers Watson's theme for his treatise was " The Influence of Variations of Diet on the Tissues and Organs of the Body." The work on which it was founded was closely allied to the researches which culminated in the discovery of vitamins.

In 1907 he was appointed Assistant Physician to the Royal Infirmary, and he continued in devoted service to this hospital for more than a quarter of a century. During these years he was recognised as a clinician of outstanding ability and a teacher of unusual distinction. He inspired succeeding generations of students by his enthusiasm, his clarity of exposition and his originality of thought. He had a deep insight into human nature and a unique capacity for imparting it to others.

His constant interest in clinical research was reflected by the number and range of his many publications during those active years. His contributions included papers on Gout and Rheumatism, the Food Requirements for

The Symptomatic Diagnosis and Treatment of Gynæcological Disorders. By M. MOORE WHITE, M.D. (LOND).), F.R.S.C. (ENG.), M.R.C.O.G. Pp. x+246, with 103 illustrations. London : H. K. Lewis. 1946. Price 16s. net.

The appearance of the second edition so soon after the first indicates that this little book must indeed have been found useful for quick reference in the out-patient department or consulting room. Written primarily to aid the doctor to make a diagnosis, it does so by reviewing the possible underlying causes of important symptoms and signs such as backache, dysmenorrhœa, vaginal discharge or genital hæmorrhage. It also outlines the therapeutic measures to be considered and describes in some detail treatment that can be applied with a minimum of apparatus and without specialised skill in the doctor's surgery or patient's home. There are also chapters on pre- and post-operative care, contraception and radiation-therapy in gynæeology. Minor alterations and additions have been made which bring the book up to date and increase its usefulness. One such is the inclusion of a paragraph at the end of each chapter to indicate the commonest errors in diagnosis and treatment under the heading " To Avoid Common Pitfalls."

Its continued popularity is certain because of the practical angle of approach to the subject and its clear yet concise and compact presentation.

Anatomical Atlas of Orthopædic Operations. By L. S. MICHAELIS, M.D. Pp. 67, with 73 illustrations in colour. London : William Heinemann, Medical Books Ltd. 1946. Price 25s. net.

This small anatomical atlas has been published in order that " surgeons will have at hand a short description and clear pictures of well-tried operative procedures." Anatomical detail is mentioned only briefly, but the position of the patient, of the limb on the operating table and the site and size of the incision are given concisely.

The line drawings are exceedingly well done, but convey in most cases little more than the skin incision and are really of no great practical help to a surgeon. Some of the illustrations in colour are excellent as far as they go, but here again it is doubtful if they would help anyone to carry out an operation. The description and figures of the operation of tendon transplantation for radial palsy are an example of this, for the former is not in sufficient detail and the latter much too crude to follow.

The operation that the author describes for a prolapsed disc must be one of the original ones and great progress in the approach has taken place since then.

The book is beautifully produced which makes it all the more regrettable that the subject matter is of such poor quality.

Human Biochemistry. By I. S. KLEINER, PH.D. Pp. 573, with 70 illustrations and 5 coloured plates. London : Henry Kimpton. 1945. Price 30s. net.

Physiological chemistry has given place to biochemistry and the biochemist has come half-way from the laboratory towards the clinic. Professor Kleiner's object is to bring home to the student the clinical aspects of biochemistry without usurping the clinician's domain and without neglecting the fundamentals. No textbook can be original ; it is built upon the work of many writers and is of the nature of a compilation of basic facts and recent advances. The present volume gives a well-balanced account of modern knowledge in this field and should be of interest to all clinicians.

Lewis's 1844-1944. A Brief Account of a Century's Work. Pp. viii+90. Illustrated. London : H. K. Lewis & Co. 1945. Free on application.

Messrs Lewis, the well-known publishers, have produced a little book giving the story of their firm since its foundation. The account contains much of historical interest in the development of medicine during the past 100 years. There are many notes on the authors whose works they published. The lending library was begun in 1852, eight years after the founding of the business, and its development is also described. The book is beautifully produced and the illustrations are excellent.

NEW EDITIONS

Refraction of the Eye. By ALFRED COWAN, M.D. Second Edition. Pp. 278, with 180 illustrations. London: Henry Kimpton. 1945. Price 24s. net.

As the author states in the preface to this new edition, the main features of the book remain unchanged, although the text has been thoroughly revised and technical aspects brought up to date.

Dr Cowan has succeeded in correlating the basic scientific facts of optics with their clinical application, in a clear and essentially practical manner.

There is much useful information for the clinician in the chapters on ophthalmic lenses, the fitting and use of contact lenses, and the management and optical treatment of ametropia.

The diagrams are clear and well chosen, and the printing and production of a high standard.

A Manual of Tuberculosis. By E. A. UNDERWOOD, M.A., B.SC., M.D., D.P.H. Third Edition. Pp. 524, with 88 illustrations. Edinburgh: E. & S. Livingstone. 1946. Price 15s.

There are textbooks on pulmonary tuberculosis to choose from, but there are few on tuberculosis, and the third edition of Underwood's *Manual of Tuberculosis* meets a need of which many have been conscious. The whole subject of tuberculosis is reviewed in an accurate and comprehensive manner. The pathology of the stages of infection and of diseased organs and tissues, the vexed questions of allergy and immunity, the varied manifestations of the disease in lungs, bones, joints, glands, abdomen, genito-urinary system and skin, complications, and methods of diagnosis and treatment are discussed with accuracy and understanding of the problems involved. The views are up-to-date, and the final sections on public measures of control, epidemiology, social medicine, and the effects of war complete a book which we recommend.

Textbook of Medical Treatment. Edited by D. M. DUNLOP, B.A., M.D., F.R.C.P.E., L. S. P. DAVIDSON, B.A., M.D., F.R.C.P., and J. W. MCNEE, D.S.O., M.D., D.SC., F.R.C.P. Fourth Edition. Pp. xvi+923. Illustrated. Edinburgh: E. & S. Livingstone Ltd. 1946. Price 30s.

After the printing of the third edition in 1944, a fire occurred at the printer's which destroyed all the type and blocks so that the present edition has had to be set up afresh. The publishers have taken advantage of this to alter the format, using a larger page which allows a shape more convenient to handle. Numerous changes have been made in the text, the chief being a new chapter on penicillin and a complete revision of the chapters on the thyroid and on venereal diseases.

The present issue of this popular work maintains the high standard of the earlier editions.

The New-Born Infant. A Manual of Obstetrical Pediatrics. By EMERSON L. STONE, M.D. Third Edition, thoroughly revised. Pp. 314. London: Henry Kimpton. 1945. Price 16s. 6d.

Dr Stone's book on the new-born infant has now survived the dangers of *its* neonatal period and has reached a third edition. Written by an eminent obstetrician of Yale University, it gives a valuable account of the obstetrical and neonatal background of the infant, and goes on to deal in detail with the care of the baby by nurse and doctor after the birth; and then gives a more summary description of the very numerous pathological conditions that may be encountered in the first month of life.

The special value of the book is its critical review of recent periodical literature on the new-born. The author again repeats what has been said by many others as to the lack of care and study given to the neonatal period by obstetrician and pediatrician alike. This gap in skilled supervision is indeed disastrous to the new-born infant; and everywhere more attention is being given now to the crowded and critical problems of this short span of life. Dr Stone's book is a valuable contribution to this important field of medical study and practice; both as a critical review and as a short manual of practice it deserves a wide circulation on this side of the Atlantic. It is hoped that in a future edition the chapter on infections will be strengthened; in its present form it is not up to the standard of the rest of the book.

Übersicht der gebräuchlichen und neueren Arzneimittel. By E. BERNOULLI and J. THOMANN. Sixth Edition. Pp. xii+568. Basel. Benno Schwabe and Co. 1946. Price unstated.

This book is rather like the *Extra Pharmacopœia* which was once edited by Martindale and Westcott, but it is published in Switzerland and therefore covers a rather different range of drugs. Switzerland is in close intellectual contact with her neighbours and this book probably gives a comprehensive and up-to-date review of the drugs used in Germany and France. Most of these are, of course, really the same as those used here, but many of the trade names sound queer. The drugs are classified according to their pharmacological action on various systems of the body, on metabolism, on infections and on skin. The final chapter deals with preparations. In many cases the name of the drug is followed by the date of its introduction. This adds greatly to the interest of the book which is to be welcomed as a guide to European drugs.

BOOKS RECEIVED

ANDREWS, GEORGE CLINTON, A.B., M.D. Diseases of the Skin. Third Edition.
(W. B. Saunders Company, London)   50s. net.

DEUTSCH, HELENE, M.D. The Psychology of Women. Volume I.—Girlhood.
(Research Books Ltd., London)   21s. net.

FEARON, WILLIAM ROBERT, M.A., SC.D., M.D. An Introduction to Biochemistry.
Third Edition . *(William Heinemann (Medical Books) Ltd., London)*   21s. net.

LEVINSON, SAMUEL A., M.S., M.D., PH.D., and ROBERT P. MACFATE, CH.E., M.S., PH.D. Clinical Laboratory Diagnosis. Third Edition.
(Henry Kimpton, London)   50s. net.

MACKENZIE, J. ROSS, M.D., D.A., and W. C. WILSON, M.V., CH.B., F.R.C.S.E. Practical Anæsthetics. Second Edition.
(Baillière, Tindall & Cox, London)   10s. 6d.

MILLARD, NELLIE D., R.N., B.S., M.A., and MARY JANE C. SHOWERS, R.N., B.S. Laboratory Manual of Anatomy and Physiology. Illustrated.
(W. B. Saunders Company, London)   5s. net.

OLKON, DAVID M., S.B., A.M., M.D. Essentials of Neuro-Psychiatry.
(Henry Kimpton, London)   22s. 6d. net.

SACHS, ERNEST, A.B., M.D. The Care of the Neurosurgical Patient.
(Henry Kimpton, London)   30s. net.

SOSKIN, SAMUEL, M.D., and RACHMIEL LEVINE, M.D. Carbohydrate Metabolism . . . . *(Cambridge University Press, London)*   —

STUTTERHEIM, N. A., M.D. (RAND.). Squint and Convergence, A Study in Di-Ophthalmology . . . *(H. K. Lewis & Co. Ltd., London)*   15s. net.

VALEDICTORY ADDRESS ON "CAN INTERNATIONAL DISPUTES BE SETTLED WITHOUT WAR—AND WILL THEY?" *

By the President, W. J. STUART, F.R.C.S.Ed.

ON this occasion the President is permitted to take the Society outside the bounds of Medicine—a good custom, for Medicine, though a wide field, is shut in by high walls. To-night, as my title indicates, I intend to take advantage of this custom.

The subject resolves itself into two questions: (1) Is there any method by which international disputes can be settled without war? To this the answer is "Yes." (2) Is there any hope of the adoption of that method by the world? Here I am unable to escape a sad and pessimistic negative.

May I first tell you how this Address, which I am delivering to-night, came into existence? The ideas are those which I held in 1919, when I put into a hamper my uniform, patched and darned in four and a half years' service, with the remark that Germany would be powerful enough to attack us again in 1943—I miscalculated by four years—and that even the old men might be needed before the end of that war. A dozen years later, in proposing the toast of the Imperial Forces at the dinner of the Overseas Medical Association, I put to-night's argument in condensed form. In my Harveian Oration of 1936 it appeared again as an example of the use of Harvey's method of investigation. Finally, on 28th January 1940, having been asked to give the second of a series of talks on topical subjects to students in the hall of the University Union, I discussed this subject in detail. Then it occurred to me that, as I had full notes of what I said, it would be interesting and amusing to put them in order and keep them, on the chance that, if I survived, I might be able to use them unchanged on this occasion, at the first meeting of this Society after the war. The surgeon can amputate part of man's body; to-night I am amputating almost six years of his fourth dimension, time. I ask you to bear this in mind as the chief interest of this Address, that I am speaking practically word for word what I said on the 28th of

* Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 7th November 1945.

January 1940, and that for the next half-hour you and I are sitting
in this hall on that same date, knowing no more than we knew then.
It is four months since the onset of war, and we are still in the stage
of our initial optimism ; the Maginot Line is regarded as impenetrable;
Dunkirk and the fall of France are in the unsuspected future ; Italy
is still uncertain as to the side which it will be expedient to support;
the Soviet, having shocked all decent nations by an unprovoked attack
upon Finland and the other Baltic States, and having taken advantage
of the attack of Germany upon Poland to stab that unhappy country
from behind, is sitting like a cynical and impassive sphinx, with a
marked inclination towards Germany ; the small nations are hiding
their heads in the sand, in the pitiful hope that they may escape
unnoticed ; the United States of America is determined at all
cost to keep out of the war ; and Japan has not yet done us the
inestimable service of forcing her into it. Such was the world at the
beginning of 1940, when this speech was made.

28th January 1940.—In an ideal world of perfect individuals the
settlement of international disputes would be easy, but it is with a
world of imperfect men and women—alas how imperfect !—that we
are faced, and with which we have to deal.

If you consider the evolution of the method of settling disputes,
amid any circumstances, whether amongst animals or men, you will
find that it always shows three stages :—(1) *The stage of the big stick
or of the jungle*—pure force, might unabashed, without the faintest
suggestion or pretence of justice. (2) *The stage of enforced justice.*
An impartial authority is set up, just decisions are made, and the
disputants accept these decisions because they are backed by irresistible
force. This is the stage which suits the world as it is to-day. (3) *The
stage of unenforced justice.* A stage only successful in a perfect
world, but Utopian to-day. The same just and impartial decisions
are given, but with no force behind them. The authority is a futile
nonentity, whose decisions the loser may disregard and the winner
must himself enforce. Hence in our world *the adoption of this stage of
unenforced justice means the inevitable return to the savage stage of
the big stick*, where the enforcement of the decision in the dispute
depends upon nothing but the force at the disposal of each disputant.

Now let me ask you to adopt the method of William Harvey.
When Harvey was unable to detect what happened at some point in
the heart-beat of the mammal, he went down to the more sluggish
heart of a cold-blooded animal, was often able to find out what he
wanted, and then came back to the speedier mammal's heart knowing
what to expect, and his difficulty was solved. We shall adopt the
Harveian method ; we shall begin, not with international disputes,
but with more simple forms of society, disputes between individuals
within a nation, and indeed still further back, between two dogs in a
backyard.

1. *A Backyard and Two Dogs.*—A dish with his dinner is set before

each dog. One covets a tit-bit on the other's dish and attempts to steal it. Then the Stage of the Big Stick appears ; a fight ensues, and goes on till one dog is forced into submission, which may be either the guilty aggressor or the innocent defender. Both have been injured and are exhausted, and, as the dishes have been overturned in the scuffle, even the victor has no dinner. But suppose that the owner, whip in hand, watches the dogs at feeding-time, and, at the first sign of theft or attack, uses the whip without mercy upon the offender. The dogs soon perceive that their master is just, but will stand no nonsense, and under this system of Enforced Justice there is peace in the backyard, and the dogs indeed are on quite good terms with one another. But if the master has no whip, and, at the first sign of a dispute, shows that he will not interfere, but with tears in his eyes appeals to all that is best in canine nature, the dogs will disregard him and go on with their fight. Unenforced Justice in the backyard has taken us back to the Big Stick.

2. *A Nation of Individuals.*—The backyard has become the nation, and the dogs are the individual members of the community. Among savage tribes disputes are settled without justice by pure force, by the Big Stick. But in civilised nations the method of Enforced Justice is adopted. Courts are set up, to which one disputant can summon another. Judges, as impartial as human nature permits, hear evidence and give decisions ; and the loser obeys without question because he knows that the decision will be enforced by the police and the whole power of the nation. The malefactor knows that the whole machinery of flying squads and scientific methods at once will be set in motion, and that neither time nor money will be spared till his capture and punishment are secured. Thus by Enforced Justice the individual, in the first case by the sacrifice of a small part of his liberty of action, in the second by insignificant taxation, secures justice, peace and safety. Note that force must be at the *immediate disposal* of the Court and police. Otherwise, when a theft or murder had been committed, the Court would require to call together representatives of all classes of citizens, who would vote as to whether any action should be taken. If it was decided to take action, a quota would be demanded from all classes, including some who sympathised with the offender, and after a few days or weeks action might begin. What hope of safety of person and goods would there be under such a scheme of Enforced Justice ? But, still worse, imagine a nation with Unenforced Justice. The police force is disbanded, a helpless Court issues its decisions, which the loser will disregard unless he knows that the winner can himself enforce it. There is no defence for the peaceful citizen against the burglar and his gang. By his own might he must defend his person and his goods, and here also Unenforced Justice has taken us back to the stage of the Big Stick.

3. *A World and its Nations.*—From a nation of citizens we have passed to a world of nations. Could a more damning accusation be

made against mankind, could anything show better how near he still is to the animal than this, that the nations are still in the stage of the Big Stick ? A dispute on any vital matter, if negotiations fail, is settled by war, in which it is a pure accident or a Divine interposition if success and justice coincide. The second stage *must* be the stage of Enforced Justice, and to that I shall return a little later. After the last war, in an outburst of mad idealism, the nations omitted this stage, and passed on to the stage of Unenforced or feebly Enforced Justice, personified in the League of Nations, a body which, as anyone who adopted the Harveian method of thought sadly knew, was by its nature foredoomed to failure, with a return, as in all premature cases of Unenforced Justice, to the Big Stick of war. The League had no armed forces *of its own* ; its decisions were slow, and determined by a vote in which the motives were too often a mixture of fear and hope, of future dangers and benefits. Each nation, with no confidence in its neighbours, suspected that, if it stood firm, it would be left unsupported to pull the chestnuts out of the fire ; and the United States of America, by standing aside from the League, made economic sanctions futile, and the success of the League and the avoidance of war alike impossible. The gangster nations judged that they could count upon the inaction of the League, and they were not mistaken. Japan, Italy and the Soviet have so acted with success, and now Germany has done the same, whether or not with equal success only the future of this war will decide.

In my Harveian Oration of 1936 I used these words :—" The League of Nations belongs to a future far beyond the stage of evolution to which man has yet attained. That stage *will* come, for the universe is governed by a God and not by a devil, and the march of mankind is on and up ; but He is a timeless God, with Whom a thousand years are as one day ; and the stage of Unenforced Justice may still be thousands of years into the future, years of which each day may be itself a millennium ; and so we have that magnificent conception but pathetic anachronism, the League of Nations, born years—thousands of years perhaps—before its time, which to-day would receive whole-hearted and enthusiastic support from none save the vultures and jackals of Ethiopia."

And now we can come back to our two initial questions :—(1) *Is there any method by which international disputes can be settled without war ?*

Our survey of the backyard, the nation and the world suggests that there is only one such method at the present stage of man's evolution, that of Enforced Justice, built on the same foundations as our Courts of Justice. It means an International Court with an international panel of judges who, without fear or favour, will in their decisions obey the dictates of conscience and nothing else. If no such men exist in the world, then indeed man is doomed and deserves his fate. The nations must disarm or be disarmed. Under the Court

there must be, not quotas from the nations, but an enormous force of men enlisted under the service of the Court itself, with a loyalty to it which, I venture to think, they would soon acquire. At suitable points these men must be stationed, with tanks, aeroplanes, poison gas and all the devilments of war.* Should a nation begin to arm, or should the Court's decision be disobeyed, these would be launched against the offender without delay, pity or mercy; and because of its inevitableness, the use of this power would never be required and there would be peace. The cost, spread over the nations, would be to each small in comparison with that of our national armaments.

(2) *Is there any hope of the adoption of this method by the world?*
Should Germany win this war—none; the question need not even be discussed. Germany is in the stage of sub-civilisation of the Old Testament Jew, and Hitler has been quick to perceive it, and to foster and use it for his ambition and purpose. The claims of the German are identical with those of the ancient Jew—a pure stock, a tribal God, a chosen people, a special destiny, a heaven-sent culture, a divine mission to disseminate it, a duty to smite opponents hip and thigh, the unprovoked invasion of a coveted land, and the massacre of its inhabitants—man, woman and child. Were it not for the tragedy, there would be sardonic humour in the fact that Hitler aped the ancient Jew, took him as his ideal and model, and then turned upon the descendants of his teacher. Should Germany win, *vae victis*; may Heaven have mercy upon us, for we shall find none on earth.

If we win, France and ourselves and any nations that may yet join us, is there any chance that we at the end of the war shall set up this Court of Justice of the Nations? By that time we shall have amassed huge armaments, otherwise defeat would have been ours. Shall we be prepared to put them on the salvage heap? Shall we be prepared to give up our hard-won success? Shall we have sufficient confidence in the judges, some chosen by our enemies, to commit our safety to their keeping? Shall we take the chance that the whole machine may be captured by some future statesman? Shall we obey the vision of the prophet Micah: "They shall beat their swords into plowshares, and their spears into pruning-hooks; nation shall not lift up a sword against nation, neither shall they learn war any more," while his essential condition is unfulfilled, "and we will walk in the name of the Lord our God for ever and ever"? Three hundred and sixty-two years before Christ there opened in the Forum of Rome a huge gulf from which the whole city was in danger. The augurs foretold that it would ever widen till into it was cast the most valuable thing which the city possessed. With feverish haste the citizens poured in their treasures and it yawned ever wider. Then Marcus Curtius, a Roman knight, told the assembled citizens that not their gold and jewels but a Roman knight in armour, mounted on his war steed, was the most precious thing which the city possessed. He spurred into the abyss,

* To this must now be added the atomic bomb.

man and horse vanished, and the gulf closed. Will the victorious
nations do this, and, with success in their hands, give it all up for an
ideal which, if successful, will confer upon the world the untold benefits
of peace, but which, alas! may fail, and end in nothing but national
suicide amid the mocking laughter of their enemies? Looking into
my own mind—am I a type or an exception? I find no Marcus
Curtius there.

I see no hope of permanent and stable peace save by Enforced
Justice and an International Court with irresistible power, but I
also see small chance of its adoption. What is the alternative? Is
there any, except that the peace-loving or peace-working nations shall
by force impose a Pax Romana for the benefit of the world? They
must include a sufficient number of the most powerful nations; they
must preserve their unity and their standards of justice; and they
must sacrifice much of their ease and comfort to maintain their fighting
forces. For a time they will do so, and then they will tire; and in
any case such a peace is one-sided, not based upon obvious justice,
and is fundamentally unstable. Sooner or later it will end and there
will be war once more. I am pessimistic enough to see a vista of future
wars, till man learns the simple essentials of self-preservation, till his
insensate madness ceases, and his nature is changed to something
higher and more divine.

With one vital difficulty we shall be faced, if this war ends in our
favour, the fate of a defeated Germany. For a time she may, and
doubtless must, be kept in subjection by pure force. But with an
efficient and powerful people this cannot go on indefinitely; yet in
her perverted manhood and distorted youth some fundamental change
must occur if she is to be admitted on equal terms into the common-
wealth of nations, which is the only final solution. *This change
cannot be enforced from without;* it must come from within. By no
compulsion or persecution can deep-seated opinions be stamped out;
these indeed are the hothouses and incubators of even a weak and
infant faith; by persecution Christianity was preserved and
strengthened. But from a study of the whole past of mankind one
striking fact emerges. It depends upon this, that man is a worshipping
animal; he must worship someone or something outside and above
himself; and, in the Freudian jargon, he is always anxious, though
often unconsciously, to transfer his super-ego to the object of his
worship. When a proud and powerful people has been defeated they
are overwhelmed, humbled, embittered, disillusioned; their ambitions
are dashed to pieces, hopes shattered, self-respect gone, with no faith
to console them, no future, no ideal to which to aspire, nothing to
worship. Sooner or later there comes forward a man who takes
advantage of the discontent, disillusionment and absence of faith of a
humbled and divided nation, and, with a new faith, a new purpose, a
new gospel of hope and a new self-respect, secures for himself the
waiting worship, and unites behind him an awakened and enthusiastic

people who will obey him even to death itself. All the teaching of the past is that this must and will happen ; the more despondent the people the more dependent are they upon their leader, and they will hear no other voice. Upon the man and his gospel depend the nation's future and its effect upon the world. To the ancient Jew Moses was such a man ; Germany has known two, Martin Luther and Adolf Hitler. By one the German nation was guided to the worship of the Absolute God, who demands the ethical perfection of a magnificent code ; by the other misguided to the worship of an imperfect man and of a fantastic personification of his own aims and ambitions, which he called Germania. To which of these two types will conform that unknown and perhaps still unborn man in Germany, and what will be his gospel ? Upon the answer to these questions will depend the future of Germany and its effect upon the world.

June 1943.—Such were my words in January 1940, and now, in June 1943, I add what is almost a quotation, at a time when we seem to have turned the corner of the war, though doubtless the most fearful slaughter of our manhood is still ahead. I have been studying again, as many of you must have done, that wonderful book, *Instincts of the Herd in Peace and War*, by Wilfred Trotter, and its insight and foresight are so uncanny that one almost forgets that it was published in 1915, near the beginning of the first great war. For the details you must go to the book itself, but in a few words, sometimes mine, sometimes his, I may indicate his argument and his advice at that time concerning Germany. Animals, men and nations which are gregarious form herds of three types. There is the Aggressive or Lupine Herd, of which the wolf-pack, the wild dog and the German nation are types ; the Defensive or Protective Herd, such as is formed by sheep, and might have been formed by the small European nations had they possessed the commonsense of a sheep ; and the Socialised Herd, where the individual altogether subordinates his own good to that of the herd, as shown by the ant and the bee, and to some extent by our nation in the government of dependencies and native peoples. " The wolf is united for attack, the sheep is united for defence, but the bee is united for all the activities and feelings of its life. Germany has modelled her soul upon the wolf's . . . already she is the finished product . . . England has taken as her model the bee, and still lags infinitely far behind the fulfilment of her ideal." But the difference between Germany and Britain almost amounts to a specific difference of the biological state.

Trotter discusses in 1915 what should be done with Germany if defeated in that war. Some people, he says, fear that to " humiliate " Germany will mean a persistent desire for vengeance and another war. This opinion of human or animal nature is not well founded. Vengeance, though vowed in excited moments to be undying, in actual fact fades out and gives way to more urgent needs and emotions. The members of the aggressive herd understand nothing but force ;

the sheep have their shepherd, but the pack of hounds has its whips. When a dog is bad-tempered, bites, and shows that it has reverted to the nature of its wild-pack ancestors, it can still be cured. But there are two things that you must not do. You must not pat its head, tell it that it is wicked to be bad-tempered, that you are sure that it did not mean to bite, and that it will be good in future and give it a bone. Nor must you give it a few cuts with a whip, when it will go away with a growl and bared teeth, and will bite you again when it gets a chance. You must thrash that dog without mercy, and go on till the growl becomes a whimper, till he knows that he has met his master, and the dog in most cases will become a decent and happy member of the household. I now end with Trotter's own words : " The animal must be left in no doubt as to who is the master, and his punishment must not be diluted by hesitation, nervousness or compunction on the part of the punisher. The experience then becomes one from which the dog is capable of learning, and if the sense of mastery conveyed to him is unmistakable, he can assimilate the lesson without reservation or the desire for revenge. However repulsive the idea may be to creatures of the socialised type, no sentimentalism and no pacifist theorising can conceal the fact that the respect of the dog can be won by violence. If there is any truth in the view I have expressed that the moral reactions of Germany follow the gregarious type which is illustrated by the wolf and the dog, it follows that her respect is to be won by a thorough and drastic beating, and it is just that elementary respect for other nations, of which she is now entirely free, which it is the duty of Europe to teach her. If she is allowed to escape under conditions which in any way can be sophisticated into a victory, or, at any rate, not a defeat, she will continue to hate us as she continued to hate her victim France." Germany will wage war after war if permitted, and will win some day, and then *vae victis*. " The foregoing considerations," Trotter adds, " are enough perhaps to make one wonder whether, after all, Western civilisation may not be about to follow its unnumbered predecessors into decay and dissolution. There can be no doubt that such a suspicion is oppressing many thoughtful minds at the present time."

These quotations are not my words, but the words of a man who was one of the wisest and most farseeing in our profession.

6th November 1945.—On the eve of this meeting I add these few sentences. Most of what I have said to-night, based on views which I have held for the last five and twenty years, was spoken almost six years ago, in January 1940, with an addition two and a half years ago. Now, in November 1945, I have not cancelled or changed a single word. Would anyone now, in 1945, challenge the accuracy of the answers which I gave to my two initial questions. The answers were obvious ; I claim no special wisdom.

1. An International Court with irresistible force in its own hands would, if honestly instituted and worked, settle international disputes

and make war impossible. This is the only method by which these objects can be achieved.

2. Such an International Court is, as I anticipated, not being instituted by the victors in this war.

What of the temporary alternative—the only alternative—which I discussed, that the victors should maintain their unity and their standards of justice, and enforce upon the world a Pax Romana? I imagined that the victorious nations, welded together by the fires of war, would for perhaps half a generation show an outward semblance of harmony; that for that time they would preserve their union under the compulsion of war exhaustion and the necessity of self-preservation; and that their decisions would be based upon justice from mere expediency, and from some attempt to fulfil those noble ideals which, amid the anxieties and dangers of war, had been committed to an enraptured but sceptical ether with much back-patting and self-approbation.

My modified optimism was mistaken. If I may use an absurdity which is only verbal, union after the war has ended before it began. Dissension and absence of mutual confidence are obvious, without even a cynical effort to conceal them. Decisions even now are being based not upon justice but upon the supposed self-interest of this Power or that. In the words which I used in 1940 and quoted a few minutes ago: " Sooner or later " (and it has proved to be " sooner ") " this peace will end, and there will be war once more. I am pessimistic enough to see a vista of future wars till man learns the simple essentials of self-preservation, till his insensate madness ceases, and his nature is changed to something higher and more divine."

This has been called the Penultimate War. If man persists in submerging that part of himself which is God-like and God-given, there will be another war, which, with all its added devilments, may well be the Ultimate—unless two individuals happen to survive, when yet another war will be inevitable!

LIGATION OF THE DUCTUS ARTERIOSUS *

By A. RAE GILCHRIST, M.D., F.R.C.P.

THE ductus arteriosus plays an essential part in the fœtal circulation for through this channel blood is driven from the pulmonary artery into the aorta. The lungs are thereby short-circuited. Blood entering the right side of the heart travels via the pulmonary artery and ductus to the descending aorta and thence to the placenta. It is well known that in a proportion of children the ductus remains patent for months or even for years before final closure takes place. It may remain patent throughout life. If it persists, a series of changes take place in the mechanics of the circulation which are of considerable interest and which may have a deleterious effect on the welfare of the individual. In extra-uterine life, if the ductus persists as a functioning channel, the higher pressure in the aorta drives a proportion of blood from the major circuit into the pulmonary artery. As a result the pulmonary artery is fed from two sources. It receives the blood expelled by the right ventricle and also arterial blood directly from the ductus and aorta. This has the effect of imposing an additional and purposeless load on the heart, particularly on the left ventricle, the output of which exceeds the right by the amount of blood entering the ductus. The pulmonary artery and its branches throughout the lungs enlarge in order to accommodate the increased volume of blood which the artery carries. In life the ductus is often a flimsy structure of greater dimensions than commonly supposed ; it usually approximates in bore to that of the aorta with which it is united.

DIAGNOSIS OF PATENT DUCTUS

Recognition of the lesion in childhood is usually simple. By the age of four or five years the very characteristic murmur can usually be recognised below the inner end of the left clavicle—a murmur to which various descriptions have been given. It is sometimes known as the humming-top murmur, the " train in a tunnel " sound, or the machinery murmur ; but the one feature which is so characteristic, and which was first described by Gibson about 1900, is the murmur's continuous quality. It runs through the whole cardiac cycle. To the trained ear the recognition of the murmur is simple and the diagnosis can as a rule be established readily by the detection of this physical sign, well entitled to the name of the Gibson murmur. It is a curious fact that the murmur only develops its characteristic continuous quality after a variable number of years. In its absence

* Read at a meeting of the Medico-Chirurgical Society of Edinburgh on 7th November 1945.

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there are other signs which may lead to a suspicion that the ductus is persistent. In a child or young person a pulmonary systolic murmur with an accentuated second sound is always suggestive, and confirmation of its nature may be obtained by the detection of an increased pulse pressure either at rest or after exercise and by the radiological appearances. As a rule by the time the age of five is reached the auscultatory signs are definite enough.

Radiological examination should not be omitted. The striking feature on screen examination is the degree of pulsation in the pulmonary artery itself and the extent of the forcible contraction of the left ventricle. Occasionally it is possible to recognise arterial pulsation in the lung roots—the so-called " hilar dance." Prominence of the pulmonary artery is not always present ; indeed, in children who may exhibit the characteristic Gibson murmur, dilatation of the main trunk of the pulmonary artery may be lacking though increased vascularity of the lung fields is usual.

The reaction of the blood pressure to physical exercise is in sharp contrast to that observed in a healthy individual. In patients in whom the ductus persists as a functioning channel the diastolic pressure often falls after exercise to an extremely low level, and the patient may then for the space of a minute or less have all the appearances associated with free aortic regurgitation—bounding neck vessels, the Corrigan pulse, and even capillary pulsation. The diastolic pressure returns within a minute to its pre-exercise level so that the characteristic reaction is shortlived. Unfortunately, blood pressure readings are difficult to make in a child under the age of five or six, when, in the absence of the fully developed Gibson murmur, a positive test would be of most value. In older children and younger adults this test may prove helpful in the elucidation of pulmonary systolic murmurs of doubtful origin.

THE INFECTED DUCTUS

From the point of view of their surgical treatment these patients fall into two distinct groups. The first is the so-called infected group about which opinion is now unanimous. All these patients should be submitted to ligation at the first opportunity. It is a curious fact that the presence of this congenital flaw predisposes to an infection in the pulmonary artery analogous to a bacterial endocarditis. On the wall of the pulmonary artery opposite the entrance of the ductus atheroma occurs, presumably as a result of the action of the forceful jet of blood impinging on the artery wall. At this site of damage and round about the edges of the ductal orifice within the pulmonary artery, vegetations form—large, fungating vegetations from which fragments are readily detached, only to be swept forward into the pulmonary circuit with the formation of scattered infarcts. Consequently these patients have signs of pulmonary involvement, hæmoptyses being common with a patchy consolidation here and there throughout the lung fields. They

have signs of septicæmia and usually yield on blood culture a *Strepto-coccus viridans*. Finally, there are local signs which unless looked for carefully may be missed. The Gibson murmur, in consequence of dilatation of the pulmonary artery, may be heard further afield than usual, the site of maximum intensity being perhaps under the middle of the clavicle rather than immediately below the sterno-clavicular articulation. This is a clinical picture which deserves to be better known as the diagnosis is frequently overlooked. As lung signs predominate, it is not surprising that acute pulmonary tubercle should be suspected. Other mistaken diagnoses are mitral stenosis with pulmonary infarcts or sulphonamide-refractory pneumonia.

The diagnosis can be established on clinical grounds alone, but blood cultures and serial X-rays can help to clear up any doubts which may arise. The recovery of the *Streptococcus viridans* from the blood, the recognition of embolic phenomena, and the local auscultatory signs over the pulmonary artery should clinch the diagnosis. As the sepsis persists the heart enlarges steadily; and as pulmonary infarcts recur from time to time serial X-rays may provide a fairly characteristic picture, the suggestive features being the progressive enlargement of the heart, the increasing dilatation of the pulmonary arc, and the scattered consolidation, advancing here and subsiding there, all of which go to make up a radiological sequence on which the diagnosis of subacute infective endarteritis of the pulmonary artery and ductus may be made with confidence. Four patients with infective endarteritis of the pulmonary artery have been under observation : three were submitted to surgical interference; one recovered. The main facts are grouped in the accompanying table.

TABLE

Four Cases of Infective Endarteritis of the Pulmonary Artery and Ductus

Case No. and Initials.	Age and Sex.	Original Provisional Diagnosis.	Duration of Infection.	Congestive Heart Failure.	Blood Culture.	Date of Ligation.	Result.
1 ; J. D.	19 M	Influenzal pneumonia	4 mths.	No	*Strep. viridans*	12.10.40	Died 15.10.40; massive pulmonary collapse
14 ; M. B.	28 F	Sulphonamide refractory pneumonia	6 „	Yes	Repeated cultures negative	30.5.44	Died 2.6.44; massive pulmonary collapse
23 ; M. G.	42 F	Heart failure and pneumonia	13 „	Yes	Not done	Not done	Died ten days later far advanced in congestive failure. Multiple peripheral and pulmonary emboli
35 ; M. S.	6 F	Recurrent pneumonia	6 „	No	*Strep. viridans*	2.12.44	Prompt recovery. Remains well eleven months after operative cure

The dramatic recovery in the fourth patient (Case 35) was a real encouragement after previous disappointments. The relevant facts of this child's illness are as follows :—

CASE 35.—M. S., a girl aged six years, was admitted to the Royal Infirmary on 23rd November 1944. She had been ill for six months, the leading features being loss of weight, listlessness, irritability, and an

irregular fever, culminating in two attacks of " pneumonia " within the three months previous to her admission to hospital. She was an undernourished child, height 3 ft. 3 in., weight 31 lb., obviously ill, with well-marked signs of a patent ductus and a patch of consolidation in the lower lobe of the left lung. She had a loud Gibson murmur, an enlarged heart with B.P. 104/44. Temperature 102°, pulse 126, respirations 34 ; hæmoglobin 54 per cent., R.B.C. 3,200,000, W.B.C. 15,000 ; B.S.R. 40 mm./hr. Spleen enlarged, no peripheral emboli, blood culture—*Streptococcus viridans*, profuse growth. With these facts to guide us the diagnosis of an infected pulmonary artery and ductus was easily made. Ligation was performed by Mr Mercer on 2nd December 1944. A blood culture taken thirty minutes before ligation of the ductus yielded a growth of 30 colonies *Streptococcus viridans* per cubic centimetre. Ten minutes after the ductal ligatures had been tied a second culture yielded a growth of 1 colony per cubic centimetre. Further cultures the same day and subsequently were consistently negative. The child had some slight respiratory distress for three or four days after operation and one further pulmonary embolism on the fourth day, but otherwise her postoperative course was uneventful. Slight aphonia and a minor paresis of the left dome of the diaphragm cleared up quickly. Her blood pressure stabilised around 110/70. Her fever subsided immediately. She gained weight and strength, made a complete recovery, and has returned to a life of full activity. Eleven months after operation the girl was well and attending school regularly with no complaints.

No one could fail to be impressed by the remarkable recovery which this child has made, particularly by the promptness with which all signs of septicæmia were abolished by the ligation. It is reasonable to suppose that had the diagnosis been established at an earlier date in the three fatal cases, better results might have been anticipated. Medical measures in themselves promise little. Surgical ligation in the infected case is the only treatment to consider. No patient with a known patent ductus should be allowed to run an unexplained fever for as long as ten days without blood cultures and radiograms of the lungs for infarcts. By such means the diagnosis will be established at the earliest date possible. Ligation of the ductus eradicates the local infection in the pulmonary artery.

THE NON-INFECTED DUCTUS

This group is composed of 36 patients ranging from the age of four to fifty-one years; of whom 21 were females and 15 males. In the majority surgical ligation may be advised with two objects in view, the first being to restore their circulatory capacity, correct underdevelopment, and improve bodily nutrition. Of greater importance, surgery undertaken opportunely plays a major part in the prevention of the serious complications to which a patent ductus predisposes the individual, the particular hazard being the development of local infection in the pulmonary artery with all the dangers of septicæmia and multiple infarcts. To a greater or less extent the long-continued

persistence of the ductus has a crippling effect and may well lead to congestive heart failure and early death.   There is every reason to suppose that successful ligation is *the* means of preventing these serious complications.

Of these 36 non-infected patients, 16 have been submitted to surgery.   In 20 patients surgery has not so far been undertaken for a number of reasons.   Of the 16 coming to surgery we have had two
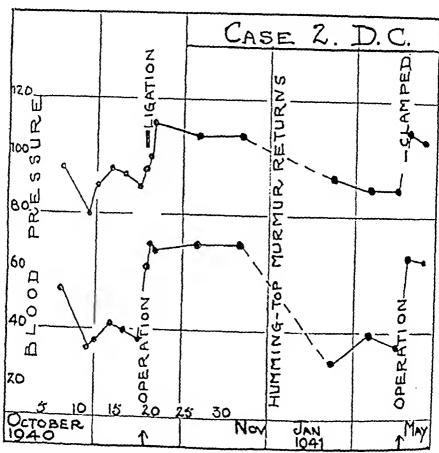
FIG. 1.—Course of the blood pressure in Case 2, a boy aged four and a half. The ductus was ligated on 19.10.40. The channel recanalised, the physical signs returned, and the diastolic pressure fell. A second ligation was done on 26.4.41.

deaths directly the result of the interference.   Both are tragedies and cast a shadow over the series.   Increasing experience should reduce the risks.   The first fatal case (Fig. 1) may be referred to in some detail.

CASE 2, a boy aged four, was an active, restless child, tiring quickly, lacking in stamina, with a heart considerably enlarged and a loud Gibson murmur.   His blood pressure varied between 90/50 and 80/34.   Ligation, recommended on the grounds of retarded development with advanced physical signs, was undertaken on 19th October 1940 after the boy had been under observation intermittently for seven months.   The usual exposure revealed a ductus about 2 cm. long and 1 cm. wide, which was ligated with a double strand of heavy cat-gut.   For two months the boy kept well when a return

of the Gibson murmur was then first suspected. His condition deteriorated, his blood pressure fell to 94/30, and on 26th April 1941 the wound was reopened and a further ligation attempted. Many adhesions made the approach difficult. The ductus, which had recanalised, was successfully isolated. After the first thick silk ligature had been securely tied at the pulmonary end, the ductus on the aortic side was wounded. Exsanguinating hæmorrhage could only be controlled by clamps which were left in position. His post-operative condition was poor. He was restless and " chesty." The forceps were removed on the evening of 2nd May 1941. The child died about 5.30 a.m. the following day from uncontrolled bleeding and general exhaustion.

This boy's death was a great disappointment. It was certainly unexpected to discover that a structure which normally obliterates itself within a few months of birth should become recanalised within two months of ligation. A further fatal case in the non-infected series may be briefly recorded.

CSAE 12, a girl aged eight, after being under observation intermittently for fourteen months had the ductus tied with two double silk ligatures on 23rd April 1944. A thin band of cellophane was packed round the ductus between the ligatures. She stood the operation well, lost very little blood, and her blood pressure rose from 126/62 to 120/80. Her general condition was satisfactory until eleven days after operation when she first developed tachycardia and later a swinging temperature with a persistent irritating cough and a sterile effusion at the left base. Blood cultures were sterile. The child's condition deteriorated steadily despite withdrawal of the effusion, sulphonamides, blood transfusions, and penicillin. She died on 26th May 1944. The persistent tachycardia, the occurrence of left interscapular pain, earache, an irritating spasmodic cough, exhaustion, and a rapidly advancing anæmia, were the chief features of an illness which, in the absence of a post-mortem examination, could only be ascribed to an infective mediastinitis.

The evacuation of fluid and blood-clot from the pleura earlier in the post-operative period and the employment of penicillin in heavier dosage at an earlier date might have averted this tragedy.

Of the 14 remaining patients in this group, all but one have received benefit in greater or less degree. Case 6, a boy of thirteen, had a large ductus 1 cm. long by 1 cm. broad, difficult to separate from the left bronchus. It was ligated by two double silk ligatures. No clips or cellophane were used. He stood the operation well but a systolic murmur was detected on the third day. In seventeen days the local signs of a patent ductus were again fully developed and the blood pressure had returned to the pre-operative level. This boy has therefore obtained no benefit. The ductus has recanalised and his physical signs are exactly as before operation (Fig. 2).

In two patients (Cases 4 and 7) the ductus was incompletely occluded, with the result that the degree of improvement, though satisfactory enough, is less than anticipated. In the remaining 11 patients the results obtained have been eminently satisfactory. The

A. RAE GILCHRIST
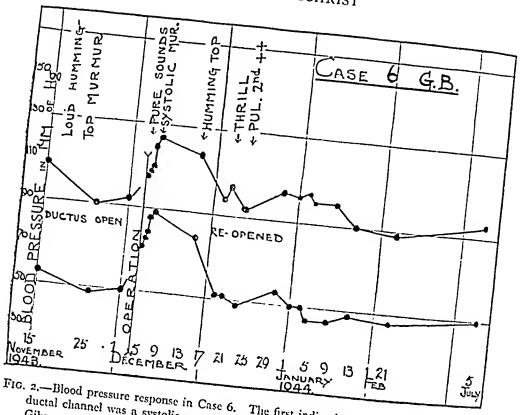
FIG. 2.—Blood pressure response in Case 6. The first indication of re-establishment of the ductal channel was a systolic murmur observed on the third day after operation. The Gibson murmur was recognised on the eleventh day. A week later the blood pressure had fallen and physical signs were then fully developed.
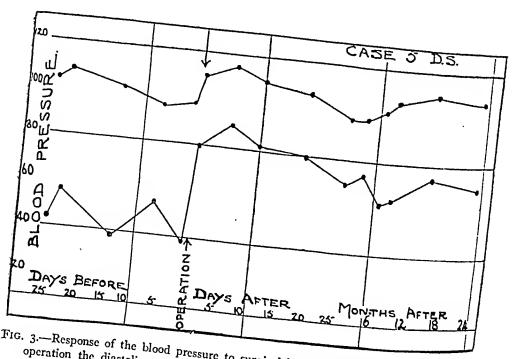
FIG. 3.—Response of the blood pressure to surgical ligation in Case 5. Two years after operation the diastolic pressure is maintained around 70 mm. as compared with a minimum of 38 mm. before ligation.

best results were observed in Case 5, a boy of thirteen, who in the two years elapsing since his ductus was ligated, has been restored to perfect health with a gain of 43 lb. in weight and 8 in. in height, and a full return of physical fitness. Radiological examination reveals a decreased vascularity of the lung fields, a shrinkage of the pulmonary artery, and a reduction in the cardiac area in relation to the size of the thorax. Blood pressure readings show a well-sustained diastolic pressure (Fig. 3).

SELECTION OF CASES FOR OPERATION

Ligation of the ductus promises much for the future welfare of these patients. It demands courage to advise surgery if the child be well and active and suffer little or no handicap, but it can be explained to the parents that the benefits to be obtained are largely those of the prevention of the killing complications, bacterial endarteritis in particular, and congestive heart failure and early death. If the child's symptoms be more evident, it is all the more permissible to urge surgery as, by obliteration of the ductus, nutrition can be restored, bodily under-development corrected, and circulatory in-capacity abolished. Thoracic surgery, reinforced by highly skilled anæsthesia, has much to offer. With the help of a thoroughly competent nursing staff, the operative risks are reduced and the prospects of a normal expectation of life for these young people greatly enhanced. With more experience of the procedure, I would now go so far as to say that nearly all children with a patent ductus should have ligation undertaken, provided that they have been observed for some time and that there is no indication that the ductus itself is closing spontaneously. In general most children should have the ductus ligated between seven and ten years of age. Over the age of ten ligation should be undertaken only if the patient shows some slight disablement, while over the age of twenty surgical interference can only be justified if heart failure threaten or if symptoms become more grave. The dangers of the operative procedure are exsanguinating hæmorrhage from a tear of the ductus, massive pulmonary collapse in the post-operative period, septic mediastinitis, clotted hæmothorax from oozing at the operative site, and of less consequence, a temporary laryngeal or phrenic paresis. With surgery confined to the non-infected ductus, the operative mortality should be under 10 per cent.

There should be no hesitation in recommending surgical ligation of the infected ductus at the first opportunity regardless of the age. With the reduction in the forceful blood-flow through the pulmonary artery, whereby fragmentation of the vegetations and contained clot is greatly reduced, the lungs presumably are better able to filter off organisms and minor emboli. Similarly, the substitution of an entirely venous environment by closure of the ductus must reduce the viability of the organisms enmeshed in the local infection in the pulmonary artery. Relieved of constant traumatisation from the high

pressure jet from the ductus, the vegetations organise and heal without the use of sulphonamides or penicillin.

The technique advocated by Touroff is a most noteworthy advance in the actual operative procedure. By subadventitial dissection on the aortic arch the risks of injury to the ductus are greatly lessened, the operative time shortened, the procedure simplified, and the liability to recanalisation reduced. The ligatures must be applied with a suitable tension, sufficient to approximate the inner surfaces of the channel, but not so tightly as to fracture the intima or media. Rupture of the coats predisposes to recanalisation. Post-operative care is of great importance. Most of these patients will have an effusion in the pleura, often a blood-stained effusion, which should not be allowed to remain within the pleural cavity as it predisposes to fibrosis and incomplete expansion of the lung. Respiratory exercises should be commenced within a few days of operation.

SUMMARY

Forty patients ranging from four to fifty-one years of age have been under observation on account of persistence of the ductus arteriosus. Its presence as an isolated defect was confirmed during life in 19 patients who came to operation.

In 4 patients there was a superimposed infection of the pulmonary artery and ductal orifice—a subacute bacterial endarteritis. Of these 4 infected patients, one, judged too ill to stand surgical interference, died a few days after the diagnosis was first made ; 2 died of massive pulmonary collapse shortly after operation ; but the one remaining patient made a brilliant and prompt recovery after surgical ligation.

There were 36 non-infected patients in the series. In 20 individuals, operation was judged unnecessary or undesirable. Sixteen were submitted to surgery—one patient on two occasions, the ductal channel having recanalised two months after the first ligation. Two deaths occurred in this surgical group. One patient obtained no benefit. Thirteen patients received material help and should be safeguarded in the future from the killing complications of this congenital defect.

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PATENT DUCTUS ARTERIOSUS AND ITS SURGICAL TREATMENT *

By WALTER MERCER, F.R.C.S.Ed.

IN discussing the surgical treatment of the patent ductus arteriosus, I should like to say that however anxious one may be about the operation, in Edinburgh there are at least two points about which we need have no worry—the diagnosis and the condition of the patient. We are always sure of the first and the condition of the patient. condition when he gets to the surgical wards, thanks to Dr Gilchrist. Indeed, as I said at a meeting of the thoracic surgeons at Liverpool the other day, " we are simply called in as plumbers to mend a leak." May I mention one other point about that meeting, and that is that through the pioneer work of Dr Gilchrist it was very interesting to hear that the English surgeons referred to the " Gibson murmur " rather than call it by one of the many other names given to it.

The area of operation is exposed by the route suggested by Touroff and Grosse, i.e. anterior exposure through the second intercostal space, though often the postero-lateral approach is used, since it is said by some workers that a better control of the vessels is got and, in the case of hæmorrhage, the pulmonary artery and the ductus are more readily controlled. The exposure is excellent. Usually a curved incision is made below the second intercostal space in order to get a valvular opening of skin and muscle covering the intercostal incision, so preventing any blow-out of the chest through a straight-through passage. Then the second interspace is divided and the left pleural cavity is opened. To enlarge the access the second and third cartilages are divided close to the sternum and the two ribs retracted, producing an excellent view of the whole area.

The first thing noted is the phrenic nerve coming down in front and, with a little more difficulty and more posteriorly, the vagus nerve—both visible through the almost transparent mediastinal pleura. Then we use an inquisitive finger—this is not a non-touch technique operation—and we are able to palpate the actual Gibson murmur. With the use of a sterile stethoscope the maximum murmur can be located to a point a little further on in the pulmonary artery itself. An incision is now made through the pleura. This is picked up just posterior to the phrenic nerve and a long vertical incision—at least two inches long—is made extending below the aortic arch and down almost to the hilum of the lung. When the mediastinum is entered it

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has to be remembered that in many cases the pulmonary artery dilates upward in an aneurysmal fashion and the ductus is hidden, so that in such cases the pulmonary artery must be dissected off the ductus and retracted downwards. There is often, too, a little pocket of pericardium overlapping the anterior part of the pulmonary artery end of the ductus. This is peeled downwards and carefully preserved. In the dissection and freeing of the ductus there are probably three methods in use. At first artery forceps holding a wet pledget of wool were used. Some used an ordinary dissector and an aneurysm needle; but I believe that forceps modified from a cholecystectomy forceps are safer and more easily controlled in this delicate operation. Actually we have a whole series of forceps of different angles and different curves up to the extent of a full half circle, all of course without any teeth. One can thus dissect carefully the region of the ductus by insertion of the forceps and opening them out time after time, until gradually the ductus is encircled. There may be difficulties because of the periarteritis and fragility of the ductus; and extreme care has to be exercised because of the danger to the ductus behind, since it is often very adherent to the bronchus and also because of the possibility of perforation of the pulmonary artery, while the recurrent laryngeal branch of the vagus nerve has to be carefully preserved and avoided.

The old type of operation simply consisted in ligating the ductus. No particular care was taken as to where the ligature was placed, and I think in a majority of cases it was put almost in the centre of the ductus, that is, between the pulmonary artery and the aorta. Recanalisation took place in some cases, and various reasons are suggested to account for this, though I do not know that any are absolutely certain. There is one obvious one: many surgeons will remember that one sometimes tied a ligature round the duodenum in olden days when a gastroenterostomy was done in what was probably an unsuitable case where there was no pyloric stenosis. The duodenum was ligated then, and one was rather amazed later to find, by X-ray pictures, that the duodenum had recanalised. This was thought to be due to a bulging of the duodenum over either side of the ligature with adherence of the overflowing margins and canalisation by erosion of the ligature. It is supposed that something similar takes place in the case of the ligated ductus because in the earlier cases published 10 per cent. of them recanalised.

Touroff had this same difficulty and he had cases of recanalisation. There are possibly other causes for recanalising, one being that the ligature was tied too loosely, and Mr Hunter at the meeting said that in certain cases there was a thrombus in the ductus and because of this the ligature could not be tied tight enough. I am not sure that I agree with this statement. Grosse, to whom great credit is due for his pioneer work in this operation, in order to prevent recanalisation put a double ligature at either end—at the pulmonary end and at the

aortic end, and in some cases injected some sclerosing fluid in that part of the ductus between the two ligatures. That evidently was not quite successful so he went a stage further, and in later cases used a cellophane strip round the ligatures. The idea of the cellophane is that it produces considerable reaction in the tissues and later, consequently, fibrosis of the encircled ductus.

Touroff has recently suggested a new method of dissecting the ductus. It makes the dissection easier and recanalisation less likely. He encircles the ductus not by dissecting round the ductus itself but by dissecting round the posterior aspect of the aorta, just adjacent to the ductus. The aorta is a strong artery and one is unlikely to do any damage to it. Touroff makes an incision in the sub-adventitial layer of the aorta above the recurrent laryngeal nerve, and burrows in this line of cleavage just on the aortic side of the junction of aorta and duct. A similar incision is made in the subadventitial layer of the aorta, proximal to the entrance of the ductus. Burrowing is continued from that side until a continuous passage is made round the posterior aspect. The whole dissection is in this way done behind the aorta and certain very obvious advantages accrue.

(1) There is much less danger and there is less likelihood of any damage to the patent ductus or the recurrent laryngeal nerve.

(2) It is much easier. It is in fact similar to a periarterial sympathectomy.

(3) There are obvious advantages in tying the ductus at the aortic end. First of all I referred to the possibility of the overflow of the ductus on either side of the ligature where the two overflowing parts come together, adhere, and later recanalise. That is possible in a fragile, thin-walled ductus, but if one of the overflowing ends is the aorta, it is not so likely that after adherence between the ductus and the thick-walled aorta canalisation will result. A further advantage is that at the aortic end the ductus is very much firmer ; there is more tissue in it and more muscle ; indeed it is more like an artery, whereas at the pulmonary end it is more venous in type. You get further advantages when you have the adventitial layer closed in your ligature as well as the ductus in that there is more tissue to resist the cutting effect of the ligature.

For all these reasons we have tried, so far as we can, to make dissections in the subadventitial layer of the arterial wall, but at any rate always as near the aortic end as possible before applying the ligatures. A ligature of braided silk has been used and usually two separate ligatures are applied. The most recent method suggested by American surgeons is ligation of the ductus at either end and division between the ligatures. Tudor Edwards said he had actually done this, but only after hæmorrhage had occurred and he had been quick enough to get on forceps.

In some cases the ductus is very short—in fact, in some cases it is

more a symbiosis of the nature of a fistula and in such cases division would not be possible. The reasonable method would then appear to be to apply a ligature of braided silk near the aortic end and put cellophane round the ligatures to produce the necessary reaction to fibrose the ductus itself.

There is a marked difference in the blood pressure before the ligature is applied. Since there are muscle fibres in the ductus itself the mechanical interference of the operation produces a certain amount of contraction and you get the ductus a little closed because of this. When the ligature is applied, the effect on blood pressure is immediate and dramatic. A pressure of 150/50 becomes 124/84 as in my first case, and frequently the diastolic pressure continues to rise for the first twenty-four hours. One to two gm. of sulphonamide is sprinkled over the mediastinum and the chest is closed in the usual manner. The operation takes rather less than one hour and the utmost gentleness is required as well as considerable patience to overcome the desire to hurry.

The histories of our cases show a continued effect on the pressure over a considerable period—indeed in all when last seen.

The possible difficulties at operation are those of exposure and freeing of the ductus, puncture of the pericardial sac, the complicating presence of troublesome glands in the arch of the aorta and, of course, always the possibility of damage to the ductus itself with serious hæmorrhage.

Complications that may arise later are hæmorrhage, though this would be very unusual; sepsis, which occurred seven days later in one case where the child had a high fever and was very ill. Fluid was aspirated from both sides of the chest and curiously enough was sterile. Penicillin, however, was given and the child recovered after some weeks of illness. The sepsis was not located. A third complication is continuing collapse of the lung which does not inflate properly after the operation, even although through an intratracheal tube inflation has been attempted at the end of the operation.

Cases have been reported by some writers, where the ductus has not been identified, where there has been an incomplete occlusion, where there has been hæmorrhage by erosion of ligature, and sometimes injury to the laryngeal nerve.

Post-operative treatment is most important though generally on lines of commonsense, but time does not permit of its discussion.

In the small series of cases that I personally have been responsible for, there was only one case of infection with subacute bacterial endocarditis, and this one, though somewhat more difficult at operation from the presence of adhesions and some fibrosis in the mediastinum, gave us at no time after the operation any anxiety. The ligation in this and other infected cases is followed by most dramatic effects, since in a matter of minutes the blood stream is free of organisms, and the temperature is normal within a very short time.

I would not like to sit down without acknowledging how much I owe to Sir John Fraser, not only for permission to help him with some of his cases, but also for the notable clinical work he has done on this subject. My thanks are also due to Dr John Gillies, because without his help I do not think I should have had the courage to do an operation of this type, and lastly, and by no means the least, to Dr Rae Gilchrist for allowing me to operate on his cases.

DISCUSSION

Mr Graham said that he regarded it as a privilege to move a vote of thanks to Dr Rae Gilchrist and Mr Mercer for their communication which, in combining the work of physician and surgeon, could not have been more suitable for the opening paper of the new session. As a surgeon he had listened with great interest to their remarks, and was sure that every one would agree that a clearer description could not have been given on this interesting and difficult subject. One of the most striking features brought out was the remarkable effect of ligation of the ductus in some cases of infective endarteritis. He wondered if Dr Gilchrist could give any explanation of the dramatic effect on the infection of the blood stream which apparently followed the mere mechanical occlusion of the ductus arteriosus.

In conclusion Mr Graham said he thought they should congratulate Sir John Fraser and Mr Mercer on the surgical skill which they had shown, and Dr Rae Gilchrist on the thoroughness with which the whole subject had been investigated.

TUBERCULOSIS UNDER A NATIONAL HEALTH SERVICE *

I. A GENERAL REVIEW

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INTRODUCTION.—In February 1944 the Government issued its White Paper on " A National Health Service,"[1] proposing a replanning of the practitioner, hospital and consultant services with the aim that every citizen should be assured of a comprehensive service of *care*, *advice* and *treatment* in matters of *personal* health. Hitherto the prevention and treatment of tuberculosis has been a function of the public health services administered by local authorities and now it is proposed to divorce the clinical part of tuberculosis schemes from direct local authority administration and marry it to the hospital and consultant services.

To discuss this first point, namely, whether the clinical tuberculosis service is a personal health service, it is important to sketch briefly some of the fundamentals of the subject, in particular, those aspects and factors which, though not part of the clinical service, have important influences on the disease.

Tuberculosis is an infectious disease distinguished by the endemic and widespread nature of the infection and the chronicity of the disease in most cases. These features make its epidemiological control a long-term problem in the individual, the family and the population at large. Thus the tuberculosis clinician has to be also an epidemiologist.

In prevention, there is the direct approach of attempting to control the infection and the indirect approach of raising the standards of environment and of individual resistance.

The control of infection has the two aspects—bovine and human infection. The control and elimination of bovine infection does not lie with the clinical tuberculosis service ; the control of human infection does.

The environmental factors are of fundamental importance, so much so that tuberculosis can be used as a social index by which the standard of living of a population can be measured. In Scotland, the mortality from tuberculosis has been falling since 1870, and no doubt the principal factors in bringing about this fall have been the improved housing, improved nutrition, and improved working conditions of the people. The tuberculosis service appeared late on the scene. In 1887, Sir Robert Phillip set up the pioneer scheme in Edinburgh, but develop-

ments were on a limited scale until the 1914-1918 war was past. The preventive influence of the service in controlling human infection might be difficult to differentiate from other factors, but the Government's White Paper [1] offers the following compliment to the service :—

" The tuberculosis service, after allowing for the indirect effects of improved housing, food and environmental conditions generally, has very tangible results to its credit over the last twenty years reflected in the improvements in the rate of mortality from the disease."

The Committee on the Scottish Health Services in their Report [10] adopted a more cautious attitude, only going so far as to suggest that the tuberculosis schemes were supplementary to the other preventive measures such as housing, nutrition, general hygiene and control of the milk supply.

MAIN FEATURES OF A TUBERCULOSIS SERVICE.—Passing to consider a clinical tuberculosis service as such, its main features should be ascertainment, treatment, rehabilitation, medical supervision and after-care designed directly to treat the individual sufferer and indirectly to prevent the spread of human infection in family and community.

(1) *Ascertainment.*—This is a better term than diagnosis as it implies more than confirming a diagnosis in a sick person and more than the receiving of a notification. It implies the search for the disease in its early stages, which means the examination of contacts in families and by mass-radiography the examination of population groups generally. These may be symptom groups or groups selected by occupation, age and sex (antenatal cases, hospital patients, nurses, young adult industrial workers, etc.).

(2) *Treatment.*—Treatment is of two kinds : (a) *Domiciliary treatment* carried out by the practitioner with the help of the tuberculosis officer and the tuberculosis nurse, usually working at and from a dispensary, unless in sparsely populated areas. (b) *Institutional treatment* in hospital and sanatorium carried out usually not by the tuberculosis officer but by hospital or sanatorium medical staff.

(3) *Rehabilitation.*—This covers (a) occupational therapy, (b) vocational training, (c) education, (d) employment, sheltered or ordinary, part-time or whole-time.

(4) *Medical Supervision.*—Until the disease is arrested the patient requires guidance in health discipline essential for self-care and the protection of others. This function falls largely on the tuberculosis officer and tuberculosis nurse. " After-care " represents the provisions other than those purely medical required for the patient and his family until health is restored.

The scheme outlined includes certain features which are not strictly medical. Occupational therapy is diversional and an adjunct of treatment. Education is not medical, but to the individual patient undergoing long-term treatment, especially the child, it is a very

important feature. Administratively, rehabilitation is regarded as having two aspects—medical and industrial. In tuberculosis the general policy of rehabilitation in two phases, one succeeding the other—medical followed by industrial—does not apply. The medical interest must continue into the phase of industrial rehabilitation, and vocational training for the tuberculous is a joint undertaking for medicine and industry, e.g. there is no point in the medical interests embarking on the training of a patient in a new vocation if industry has no job to offer at the end of it.

In considering the future organisation of the purely medical or clinical side of the care of the tuberculous, it is necessary before passing to detailed discussion of the service to emphasise that tuberculosis is an exceptional disease in that any reformed clinical service will not be complete unless it has definite and secure links with the other important features of prevention and treatment. These links are to the agencies of social environment (such as the local authority in regard to housing, hygiene and health propaganda), to the national insurance scheme in relation to financial security whilst the patient is incapacitated, to the rehabilitation schemes of industry in restoring the patient a livelihood, to the education interest in providing for the long-term child or adolescent patient a course of education as good, if not better, than would have been available in health. Sound education is essential as a wage-earning weapon to offset physical disability resulting from the disease.

Finally, no tuberculosis service would be complete without provision for laboratory services, research and medical education.

PRESENT ADMINISTRATIVE STRUCTURE OF THE TUBERCULOSIS SERVICE.—Tuberculosis schemes in Scotland are administered by the major local authorities—thirty-one counties and twenty-four large burghs. Tuberculosis is dealt with as an infectious disease under the powers conferred by the Public Health (Scotland) Act, 1897. It is considered that, apart from after-care, the local authorities in Scotland have adequate powers under the 1897 Act to administer a comprehensive scheme of prevention and treatment. Some of the authorities have combined for public health administration and administer their tuberculosis schemes as part of the joint public health arrangements (e.g. Aberdeen County and City with Kincardine County; Inverness County and Burgh; Renfrew County and Port Glasgow). Others have formed joint boards for the institutional treatment of tuberculosis, e.g. the joint boards of the Lochmaben Sanatorium for Dumfries and Galloway, and of the East Fortune Sanatorium for the Lothian and Border Counties.

The tuberculosis schemes as administered by the local authorities combine the essentially personal clinical service with the other functions such as notification, bacteriological examinations, disinfection, re-housing, propaganda, etc. Defining the clinical service as a personal one does not necessarily warrant its administrative inclusion in a

new scheme for a comprehensive hospital and consultant service unless it can be shown that the proposed new administrative structure would increase efficiency and benefit the patient and the community.

Criticism of Present Tuberculosis Schemes

More than one critical examination of existing schemes has been made in recent years, in particular, reports by Lissant Cox,[4] the Joint Tuberculosis Council,[9] and Medical Planning Research.[6]

(1) *Too Many and Too Small Administrative Units.*—The first point of criticism is that the local authorities are mostly too small to carry an efficient and comprehensive service to meet modern standards and that, with few exceptions, they have not used their powers to combine into units of adequate size. Only the larger authorities have been able to keep pace with modern developments and there has resulted an uneven progress throughout the country such that now the quality of the service is variable between one area and another. The service is hampered by the fact that any development has to be interpreted to a multiplicity of lay authorities before progress can be made.

The Joint Tuberculosis Council consider that the minimum administrative unit should deal with a population of 250,000. The fundamental criteria for an administrative unit must be the capacity to carry a sufficient quota of whole-time specialist personnel, a sufficient and balanced quota of hospital and sanatorium accommodation, together with adequately equipped clinics.

Scotland suffers more than England from a multiplicity of small local health authorities. Apply the minimum standard of 250,000 to Scotland, only four existing administrations qualify—Lanark County, the Aberdeen Regional Scheme, Glasgow and Edinburgh. Lissant Cox suggested that for Scotland a regional system of administration was necessary. The Committee on Scottish Health Services had earlier advocated regional arrangements of institutional treatment and the claim that dispensary work should be associated with the institutional side leads to the White Paper proposals.

During the war the Emergency Hospital Service in Scotland has operated on a *regional basis* and the grouping of populations has been as follows :—

Northern Region	.	.	.	.	226,500
North-Eastern Region	.	.	.	.	455,400
Eastern Region	.	.	.	.	684,500
South-Eastern Region	.	.	.	.	802,900
Western Region	.	.	.	.	2,841,200

There is general agreement that regional arrangements of the hospital services in Scotland are desirable. Assuming the country were divided according to the wartime grouping of the Emergency Medical Service, each region, apart from the North, would make up more than

one minimum administrative unit. The Northern Region illustrates the geographical difficulties of planning a medical service. Administrative arrangements which may be ideal and also practicable in a populous area may require modification in a sparsely-populated area.

If 250,000 is a minimum, is there an optimum ? The Joint Tuberculosis Council suggest that a population of one million is desirable for a really comprehensive service. The regional groupings in Scotland are uneven. Half the population is to be found in the west and in that region there would be scope for sub-regions and units convenient to accustomed centres of populations. In the other regions there might be advantages in affiliation between one region and another for certain purposes.

(2) The second point of criticism is that the tuberculosis service has been *divorced too long from general medicine*. The Joint Tuberculosis Council state that tuberculosis work is mainly clinical and must not be divorced from the other branches of clinical medicine. The Council state " Hence, it is vital that the tuberculosis service be a part of the hospital plan and not in any sense an ' attached ' service." This seems to leave no doubt that it is the considered opinion of the Council that the tuberculosis service should go in with the new hospital schemes. The Council also state that " a satisfactory standard of work will not be achieved in all areas until Tuberculosis Officers are able to take their place alongside consultants in other branches of medicine."

(3) Even within the service itself there is a *division of clinical interest*. On the one hand, there is the tuberculosis officer and tuberculosis nurse associated with the dispensary work and domiciliary treatment and, on the other hand, the hospital and sanatorium physician and nurse associated with the institutional treatment. The tuberculosis officer as a rule (there are exceptions) takes no part in the institutional work and, in the smaller authorities in Scotland, commonly combines his work with other Public Health duties. In the natural course of events the experienced tuberculosis officer may be lost to the subject if he chooses promotion in the field of public health. On the institutional side the experienced clinician has the opportunity of remaining associated with the subject although he may have added to his functions a certain amount of hospital administration.

On this dichotomy of medical work, the Joint Tuberculosis Council pronounce that " the tuberculosis service is essentially one in which team work is indispensable. The clinic, the institution and the after-care service must function as an entity." At present the tuberculous patient passes through the hands of two experts in tuberculosis, the tuberculosis officer then the sanatorium physician, and finally the tuberculosis officer once again. Would it be fair to say that the tuberculosis officer has full knowledge of the social circumstances of the case, but his clinical knowledge of the patient has to be, to a large

extent, second-hand, derived from the sanatorium physician, and the sanatorium physician has first-hand knowledge of the patient's clinical state and second-hand knowledge of the social conditions? With *a unified clinical service* this " compartmentalism " could be removed and the tuberculous patient would throughout be guided by one medical consultant or medical unit knowledgeable in both the social and clinical aspects of his case. The tuberculosis physician requires to be knowledgeable in chest conditions other than tuberculosis in order to exercise the functions of differential diagnosis and it is a point for discussion whether he should not also undertake the treatment of long-term cases of chest disease other than pulmonary tuberculosis.

(4) *There is also a divided interest in nursing.* On the one hand, attached to the dispensary and domiciliary side, is a highly specialised staff of health visitors, tuberculosis nurses, or in rural areas, district nurses, who have had special instruction in tuberculosis. Broadly, the domiciliary and dispensary work is carried out by senior nurses who have had a general training before specialising in their work. On the institutional side, the sanatoria and tuberculosis hospitals have hitherto been outside the field of nursing training, except in the case of the fever hospitals recognised as training schools in which the nurse has had the opportunity of graduating into State-registered nursing. Otherwise tuberculosis nursing has tended to be a blind alley unless for the larger sanatoria which have undertaken training for the certificate of the Tuberculosis Association. The tuberculous patient requires a high degree of nursing care and there is no doubt that under modern conditions, training in tuberculosis nursing would be of value to any nurse hoping to graduate in the profession. There is much concern at the present time that attention should be given to the social conditions of a patient, so much so that a new subject has been created (or is it an old one under a new label ?) called " Social Medicine." One cannot imagine a better exercise in social medicine than the study and care of a tuberculous patient.

What is to be the future of tuberculosis nursing ? Is it to become part of general training or a post-graduate speciality for the general trained nurse ? A scheme of training for the assistant nurse is proposed which would be made up of the nursing of the chronic sick and the tuberculous. If this is to be the only career a nurse entering a tuberculosis institution is to have, it may mean that, for the future, institutional work in tuberculosis is to continue at least as a by-way of nursing, if not the blind alley it was previously.

(5) *Dispensaries.*—It is proposed in the White Paper that, for the future, tuberculosis dispensaries should be associated with a general hospital and preferably situated in the hospital. This would facilitate its use as a centre for the differential diagnosis of chest diseases generally. The Joint Tuberculosis Council suggested that in addition to such main dispensaries with facilities for full investigation there should be smaller consultation centres on the periphery of an area.

There should be strategic placing of peripheral centres to serve as " filling stations " for cases of artificial pneumothorax.

(6) *Institutional Treatment.*—There is no doubt that the most urgent need of the tuberculosis service is a sufficient quota of institutional beds to treat adequately patients already known to be suffering from the disease.

(a) *Number of Beds Required.*—The first point to achieve is an adequate number of beds. It is appreciated this is going to hinge largely on the recruitment of nursing staff but it is necessary to state requirements. It has been usual to estimate needs on the ratio of one bed per annual death. The Joint Tuberculosis Council now propose for the country as a whole an absolute minimum ratio of 3 beds to 2 deaths per annum. In Scotland there are already in use 6000 beds representing a ratio of 3 to 2, and with shocking waiting lists there is no doubt it would require a ratio of 2 to 1 to meet the problem and it is this ratio the Scottish Hospital Surveyors propose.[11] It might be argued that the war-time increase is likely to fall ; but on the other hand with the increasing use of modern methods of ascertainment such as mass radiography, the demand for accommodation will probably continue on the ratio suggested. Where intensive programmes of case finding are undertaken, *e.g.* Detroit, the authorities find a ratio of 2 to 1 necessary. Indeed, Chadwick and Pope,[3] in discussing the ideal tuberculosis scheme, calculate that the ratio should be $2\frac{1}{2}$ beds per annual death on the assumption that there is in any community 10 cases per annual death, and of this number 25 per cent. at a time need institutional care.

Scotland is now faced with a critical situation in that the country has been left a sad legacy of war in the spread of tuberculosis. Important preventive factors such as housing may take time to operate. As a short-term policy of prevention the provision of adequate institutional accommodation is the biggest contribution that could be made.

(b) *Types of Institutions.*—Before discussing the main problem— the treatment of the pulmonary case—consideration has to be given to the institutional care of other types :—

(i) *Non-Pulmonary Tuberculosis.*—The bone and joint group require orthopædic attention. Should such cases be treated in orthopædic hospitals by orthopædic surgeons ? If so, should the tuberculosis officer be associated as a consultant to such hospitals? Alternatively, should the cases be treated in sanatoria with the orthopædic surgeon visiting in the capacity of a consultant ? Hovering in no-man's-land there is the combined case with an open lung lesion. It has not been suggested that such cases should be treated in the orthopædic hospitals. Treatment on sanatorium lines is necessary. It has been proposed that there might be special institu-

tions set up for such cases on neutral ground as it were, between the orthopædic and sanatorium camps, but probably this would mean over-centralisation. A sanatorium is probably the best place for such cases.

The genito-urinary cases merit the attention of a specialist surgeon. Should such cases be treated in ordinary sanatoria with a surgeon as a visiting specialist or centralised in selected hospitals or sanatoria as far as possible?

(ii) *Lupus.*—Although relatively small in number the lupus patients must not be forgotten in the replanning of the tuberculosis service. This form of the disease requires the provision of special centres for treatment. It is a curable disease with early diagnosis and persistent treatment. In Scotland there are two special centres providing Finsen-Lomholt treatment—in Edinburgh and in Glasgow. Dr Robert Aitken,[2] the physician in charge of the Edinburgh Centre, discussing this problem, suggests that in each region of Scotland there should be a centre properly equipped and associated with a teaching hospital. The centre should have beds available so that patients from some distance may have the opportunity of intensive courses of treatment. Lupus patients are not always well received by other patients and would probably be better in small auxiliary units and not mixed with others.

(iii) *Childhood Tuberculosis.*—Facilities for the observation and treatment of children have to be considered. The investigation of childhood tuberculosis might with advantage be associated with children's hospitals. The cases that require treatment can either be treated in sanatoria or in special convalescent institutions. Is it undesirable that such children should be treated in sanatoria and should special arrangements be made for them?

(iv) *Pulmonary Tuberculosis.*—Coming to the main problem—pulmonary tuberculosis—apart from not having enough beds, another point to consider is the nature of the institutions required.

At present only the larger authorities, those who have combined and the voluntary agencies, provide *ad hoc* sanatoria of a size capable of providing the full range of treatment modern conditions require. In Scotland there are twenty-one institutions or units with over 100 beds, ten with 50 to 99 beds, and fifty-four with under 50 beds, making a total of eighty-five institutions providing 6500 beds (500 are without staff).

It is usually considered that a sanatorium should have at least 100 beds and possibly not more than 300. The large proportion of small institutions in Scotland reflects the origins of the service in that the local authorities used the hospital resources available to them in the early days, namely, the fever hospitals. Although it may not be possible under modern conditions to provide a full range of treatment in the small institution, it does not follow that it cannot serve a useful function in the general scheme. Lissant Cox considers there is

nothing wrong in having a proportion of small institutions if they are staffed by the tuberculosis team and affiliated to the other institutions in the scheme.

A war-time development has been that certain of the larger sanatoria were selected for expansion into large general hospitals to serve the emergency hospital needs. Their situation had strategic value, and, in addition, it is a compliment to their equipment that they were capable of this development. Now these institutions present themselves in the " demob." suit of a large hospital of 800 beds or more. Would they make sanatoria in this form ? In addition, the Department of Health for Scotland erected in the country areas large emergency hospitals and in some of these hospitals there are now tuberculosis units operating similar to the nests of tuberculosis beds which have continued to function in the expanded sanatoria just mentioned. If a proper quota of beds is to be established quickly, it will be necessary to decide how far the institutional treatment of tuberculosis can be met by using part at least of the expanded hospital resources left over from the Emergency Medical Service. Hospital surveys [11] have been carried out which give a complete picture and offer suggestions on the fitting together of a post-war mosaic of hospital services in each region. It will be necessary to consider certain features if efficiency in planning the institutional facilities for tuberculosis is to be achieved.

The first point is that the tuberculosis officer or physician should have under his charge in a general hospital beds for observation and investigation, together, possibly, with a number for initial admission. Location in a general hospital will facilitate his having full resources for the investigation of his cases and be convenient to his other work. Secondly, in the country areas, the large hospitals, either the expanded sanatoria or the *ad hoc* emergency hospitals of the Department of Health, may be set up to function as " country general hospitals." [11] Should tuberculosis units be incorporated in such country general hospitals ? If so, should they be hospital units or sanatorium units ? It is doubtful if the atmosphere of a large general hospital, even in country surroundings, is likely to lend itself to sanatorium treatment in its proper sense. Hospital units might be set up in the country general hospitals and linked to existing sanatoria in the same area. Patients would have their period of bed rest in the hospital unit and then, when ambulant, would graduate to the associated sanatorium still under the same medical supervision if the senior tuberculosis physician were attached to both institutions. This two-phase system which has been carried out in Ayrshire has certain advantages.

All patients in the hospital unit are in the same stages of treatment, and ward management is easier. In the sanatorium the majority of the patients are in a phase of treatment where they are able to take full advantage of the special facilities and amenities provided. Proper *sanatorium care embodying the first stages of the patient's rehabilitation*

is no easy matter. It is a specialised task probably better attempted in the *ad hoc* sanatorium than in the confines of a large general hospital. Houghton,[8] in a discussion on rehabilitation, has made the following comment on the difficulties of sanatorium care :—

" There is in the dictionary a word . . . even uglier than ' rehabilitation.' That word is ' hospitalization,' by which is meant . . . the state of affairs supervening when an individual has been segregated in a santorium for many months or in some cases even years, cut off from normal contacts, encouraged to be immobilized and to refrain from activity during which time he is waited on hand and foot and serious personal effort has to be discouraged. The result so often is that the individual loses initiative and confidence and any real capacity for work. . . . Those of us who work in sanatoria were threatened . . . with another form . . . to fill in at the end of sanatorium treatment, stating just what the patient is capable of undertaking in the form of work. How unfortunate it would be if we were to fill in that form something like this : ' This man has been in the sanatorium so many months or years. He has occupied his time strolling around the sanatorium grounds. He was persuaded to do a little knitting. He has made some leather bags to keep him in cigarettes and he plays a very nice game of snooker.' . . . I think it would be felt to be useless to bring such an individual to a machine or even to introduce him to a moderately well-paid job, because he would have lost his initiative for work. . . .

" I believe the secret of rehabilitation is controlled initiative, but I am afraid so often both these factors, control and initiative, are missing."

(v) *Thoracic Surgery.*—It is the view of the thoracic surgeons [7] that their speciality should combine the surgery of pulmonary tuberculosis with that of other chest conditions, and that thoracic units should be established in association with teaching centres. It is economical in personnel and equipment for a thoracic unit to treat non-tuberculous as well as tuberculous chest conditions and to serve areas larger than the administrative tuberculosis unit. As regards pulmonary tuberculosis, what should the division of labour be between the thoracic surgeon and the tuberculosis physician ? Probably major surgery should be done at a thoracic unit and minor surgery carried out at the individual hospital or sanatorium. In planning thoracic units, it will be important to determine what should be the optimum stay of a patient after a major operation, bearing in mind the duration of the special after-care which is necessary.

(vi) *Pleurisy Units.*—To assist local authorities in institutional treatment the Department of Health have instituted as an emergency arrangement pleurisy units which have been operated on the same lines as the Ayrshire Scheme of a hospital phase for investigation and bed rest followed by a convalescent phase in an auxiliary hospital

for treatment on sanatorium lines. Should such units be projected in the new service ?

Medical Education.—Heaf and Williams [5] for the Tuberculosis Educational Institute have stressed the need for tuberculosis to be given greater attention in undergraduate instruction, proposing that there should be associated with each teaching hospital a tuberculosis dispensary and that there should be tuberculosis beds, both pulmonary and non-pulmonary, in one or more of the hospitals constituting the teaching centre, provided there is a chest physician or orthopædic surgeon in charge. The Institute suggest that tuberculosis physicians should be appointed to medical schools and that students should be attached to the main dispensaries as clinical clerks. In addition students should receive instruction at a sanatorium including facilities for a period of residence so that a proper understanding of sanatorium care can be acquired.

CONCLUSION.—Having discussed the various features of the clinical tuberculosis service planned for incorporation in the hospital services, one comes back to the point that in any new administration there must be proper association with the other agencies of prevention and treatment. Certain functions, it seems, will still rest with the local health authority, such as notification, disinfection, housing, and health propaganda. Efficient co-operation between the new clinical service and local health authority will be essential.

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TUBERCULOSIS UNDER A NATIONAL HEALTH SERVICE

II. With Special Reference to Rural Areas

By CHRISTOPHER CLAYSON

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INTRODUCTION.—Dr Westwater has discussed the problems of tuberculosis under a national health service with the great advantage of one privileged to have a general view of the whole tuberculosis service in Scotland. I am writing as one primarily interested in the organisation of the tuberculosis service in a wide country district.

There can be little doubt that in past years Sir Robert Philip's scheme for the control and eradication of tuberculosis was more fitted for the needs of big cities, and the application of the same fundamental principles to rural areas was surprisingly difficult. But given legislative approval of certain general indications in the White Paper on a National Health Service (1944), there seems little reason why rural areas should not have just as efficient tuberculosis services as the large towns.

THE SIZE OF THE ADMINISTRATIVE UNIT.—It seems that there will be two types of administrative unit : one which is large enough to run a complete scheme on its own, and the other which is not. The population of the former has been variously estimated from 500,000 to 2,000,000, though it is interesting to note that the Medical Officer of Health of no less a city than Manchester (770,000) has doubts as to whether it is large enough to run an economic and efficient tuberculosis service, good though its present service is. The minimum population of the smaller scheme has been suggested at 250,000 by the Joint Tuberculosis Council, and in such schemes a liaison will be needed with the thoracic unit of a very large centre, and with whatever rehabilitation scheme such a centre may develop.

It is clear that this population figure of 250,000 cannot possibly apply to Scotland without imposing absurd travelling distances on tuberculosis physicians and nurses. In the south-western sub-region for instance, 2,500 square miles would represent an area larger than one visiting physician could efficiently cover. Nevertheless with a population approximately 150,000, I am satisfied that all the essential criteria of an efficient service could be met given the liaison with the regional centre.

But in the Highlands and Islands the problem is much more formidable. The population concerned (226,500) is only half as much again as in the south-western sub-region, but the area to be covered is between four and five times as great. It is clear therefore that great flexibility will be necessary in devising the schemes for the tuberculosis service in country districts.

But whilst in the Highlands the desired scheme will be prepared at the regional level, provisions for other areas having somewhat similar problems can best be made at sub-regional levels. Each sub-region should have a large measure of autonomy in preparing its own scheme if the rural tuberculosis service is at last going to come into its own.

It must be admitted, however, that some form of central control may be needed to ensure certain minimum standards. In the past it has been found that the annual tuberculosis expenditure ratio per 1000 population in one authority might be five times what it was in another. The discrepancy between these figures is unduly wide and has in most instances operated against the efficiency of the rural tuberculosis services.

THE STANDARD NEEDED FOR BEDS.—It is unnecessary to discuss at any great length the number of beds needed for the tuberculosis service in country districts. In his general statement Westwater has recorded the standards variously suggested, and since they are related to the annual number of deaths the figures will closely follow the requirements in both urban and rural areas.

Nevertheless it is somewhat surprising that the Joint Tuberculosis Council (1944) should consider that 3 beds per 2 annual deaths is a suitable minimum figure. Scotland already has found this number inadequate. It may further be doubted whether the Scottish Hospital Surveyors' (1945) figure of 2 beds per annual death is enough. Dumfries and Galloway had this number of beds in use for some years before the nursing shortage led to the closure of part of the hospital, and it was never possible to overtake the waiting list. *The Report on Post-War Hospital Requirements for Dumfries and Galloway* (1945) took these facts into consideration and stated that 200 institutional beds were needed for all forms of tuberculosis, equal to 2½ beds per annual death. This figure was based on the number of patients treated, the average size of the waiting list and on an estimate of the probable number of pulmonary cases which would in the future be discovered by mass radiography. The figure arrived at agrees with that adopted after a different type of calculation by Chadwick and Pope (1942).

THE SCOPE OF THE COUNTRY SERVICE.—The consideration of future developments in the tuberculosis service is based on the statement in the White Paper that the new Hospital Authority will be charged not only with the sanatorium but with dispensary work as well. Where a Health Authority is so large that it does not need to combine with another to form a hospital board no great change is necessarily involved. But in smaller authorities and especially in country districts interesting new developments are opened up.

In most country districts there are no tuberculosis dispensaries as such. In some areas the sanatorium attempts to overtake the functions of the dispensary. Thus in Dumfries and Galloway Sanatorium an active out-patient department has been developed along the usual

dispensary lines. The department is a receiving house and a centre for diagnosis, where patients recommended by their own doctors through the medical officers of health of the combining authorities, attend for examination. It is a clearing-house whence patients are either admitted to the sanatorium or, as a recent development to meet the needs of difficult times, to a small peripheral (infectious diseases) hospital under the control of the appropriate medical officer of health. Where diagnosis is incomplete the department is also a centre for continued observation ; and in co-operation with the medical officers of health of the combining authorities, it is a centre for contact examination. It is also a centre for follow up of discharged cases and for active curative treatment. In other words the sanatorium is in a very real sense a dispensary as well and fulfils most of the functions described by the originator of the dispensary movement. But under present-day methods it is not a centre for domiciliary supervision or care work.

To what extent country sanatoria in general work along these lines is uncertain. Some appear to adopt a similar practice whilst others purposely avoid doing so in order to concentrate their full resources on their institutional functions. But in either case there still remains the division of clinical interest between the sanatorium physician and the tuberculosis officer which was commented on by Westwater above. This partition goes deeper in many country districts than it does in the larger authorities since most country health authorities do not employ a full-time tuberculosis officer. The division of clinical interest therefore is between the sanatorium physician and the medical officer of health, and owing to the wide responsibilities of the latter, the arrangement may be a more justifiable target for criticism in the country than in big towns.

THE NEW HOSPITAL AUTHORITY.—In the new health service it seems that this dichotomy will be avoided by grouping the hospital and out-patient clinic services under one administration. It is here that flexibility of arrangement is needed in different parts of the country in order that each region and sub-region can most effectively serve its area. In general, however, this unified service should be placed in charge of the tuberculosis physician based on the sanatorium (or on the principal tuberculosis institution if there are more than one) serving the area. The physician would be ultimately responsible for the welfare of the tuberculosis subject throughout his district. But he would have to assist him one or more out-patient (dispensary) tuberculosis physicians according to the size of his area. So far as practicable the Joint Tuberculosis Council recommendation that this type of practitioner be of consultant status, should be fulfilled.

THE SANATORIUM.—On this basis, the relationship of the tuberculosis physician to the out-patient physician requires clarification. The recommendation in the White Paper that the dispensary physician should have " charge of and direct access to sanatorium beds " is not necessarily the best way of achieving the object in view, namely,

an efficient tuberculosis service. In a small service divided control of the sanatorium could arise which would be undesirable. The Joint Tuberculosis Council (1944) comments as follows on the proposal: " It would not be in the interests of adequate institutional treatment of patients that existing sanatorium beds should be divided among the visiting tuberculosis officers as proposed in the White Paper."

The Joint Tuberculosis Council proposes as an alternative arrangement that the tuberculosis officer should have beds under his direct control, preferably in a general hospital, for the diagnosis and assessment of his cases. After complete assessment the patient could be discharged home or admitted to the sanatorium as required. Clearly he could not remain any longer in the general hospital than absolutely necessary. On the whole this proposal cannot be regarded as entirely satisfactory.

Neither of these suggestions seems quite to solve the problems of the country tuberculosis service, but the former, suitably modified to meet the objections of the Joint Tuberculosis Council, would seem to be the more promising.

The sanatorium superintendent, who as senior physician would be the head of the service, would have such resident assistants as the size of the institution requires and such out-patient (non-resident) assistants as the population and size of the area require. The latter would spend the greater part of their time in domiciliary and clinic work, each in his own sub-area, but some of their time would be devoted to visiting the sanatorium for the diagnosis and assessment of their cases. Whilst attending the sanatorium their access to beds would be free, but ultimate control would remain vested in the sanatorium physician to whom the assistants, resident and non-resident, would alike be responsible. In this way divided control would be avoided.

THE DISPENSARY.—The development of out-patient work in a country tuberculosis service may take place either at the sanatorium or at the general hospital for the area. I have referred above to the fact that in Dumfries and Galloway this process has hitherto taken place in the sanatorium. But the *Report on Post-War Hospital Requirements in Dumfries and Galloway* recommends the establishment at the general hospital " of an out-patient clinic dealing with tuberculosis and allied conditions under the charge of the tuberculosis physician, replacing the out-patient clinic held at the sanatorium." This is in line with modern developments, and in any area an assistant physician might be given responsibility for the work provided he were of specialist status.

PERIPHERAL CLINICS.—Quite apart from the central dispensary work, a wide rural area will require a suitable number of peripheral clinics. In a unified clinical service these small dispensaries would remain part of the ultimate responsibility of the tuberculosis physician but would be placed in the direct charge of the out-patient physician of the area.

DOMICILIARY VISITATION AND CONSULTATION.—The out-patient physician will normally be responsible for domiciliary supervision of patients in co-operation with the family practitioner. In the forthcoming health service domiciliary specialist consultations will be provided, but wherever possible should be delegated to the out-patient physician.

THE DIVISION OF RESPONSIBILITY BETWEEN THE HOSPITAL AUTHORITY AND THE LOCAL AUTHORITY.—Where a number of health authorities continue to form a joint board there inevitably arises a division of functions between the hospital service and the medical officers of health. This cleavage must occur somewhere and, short of obliterating local authority boundaries, seems inevitable. But there may be much differences of opinion as to where the functions of a joint service should end and those of a medical officer of health should begin. Following the indications of the White Paper the allotting of dispensary and clinic services to the hospital authority will limit the functions of the medical officer of health in the new tuberculosis scheme. It seems that the future Hospital Authority dealing with tuberculosis would be responsible for (1) sanatorium treatment, (2) dispensary practice, either at the sanatorium or at the related general hospital, and at the peripheral clinics where these exist, (3) care work at home for the family unit, including medical aspects of the financial allowances scheme. The Medical Officer of Health of the Local Authority would retain control of (1) notification, (2) housing, (3) administrative aspects of allowances, and possibly (4) home nursing.

This may not be an ideal arrangement, but most tuberculosis physicians would probably view with satisfaction the increased facilities for the follow-up of their patients afforded in the new plan. But it is not too much to say that the success of the whole scheme will largely depend on the out-patient physician. It is he who would have to maintain cordial relationships with the family practitioner in the patient's own home, and with the medical officers of health—probably at the peripheral clinics. It is at these clinics where the interests of the out-patient physicians and the medical officers of health overlap. Housing, financial allowances, home comforts, and nursing, and the problems of after-care in general afford ample scope for co-operation between the new health service and the local authority. It would be as unfortunate as it is erroneous if the impression grew that the medical officer of health was of little importance in the new tuberculosis scheme.

THE TUBERCULOSIS NURSE.—In future it is desirable that part of the orthodox training of the student-nurse be spent in the study and practice of tuberculosis nursing. In a health scheme consisting of a number of affiliated hospital units steps should be taken to ensure that each unit contributes its share of nursing training, and rotation of junior nursing staff should be planned accordingly. The post-graduate nurse engaged in tuberculosis work will, it is hoped,

take the Tuberculosis Association Certificate or its officially recognised equivalent.

THE VISITING NURSE should be a fully trained nurse with, if possible, a health visitor's certificate and a special diploma in tuberculosis. Being normally on the personnel of a dispensary service she will be on the staff of the hospital authority working under the general direction of the out-patient physician. But since adequate numbers of this type of nurse will not be available in country districts the out-patient physician will require the assistance of the district nurse. I have no special knowledge of what the future of the Queen's Institute of District Nursing may be, but presumably their assistance in the tuberculosis service would be sought through the Medical Officer of Health.

This connection of the district nurse with the scheme is important and steps should be taken to provide her with a special interest in tuberculosis. Refresher courses should be provided for Queen's Nurses at the appropriate sanatorium. The method was carried out for some years before the war at Southfield Sanatorium, Edinburgh, where the Queen's Nurses of the County of Inverness (amongst others) received training courses of three weeks' duration with advantage to themselves and to the tuberculosis service of the county. Similar movements might well be carried out in all country districts.

ORTHOPÆDIC TUBERCULOSIS.—The tuberculosis physician in a rural area will probably find that it would be most practicable to treat his orthopædic cases in the sanatorium, with the co-operation of a visiting orthopædic surgeon who would be a consulting member of the sanatorium staff. The alternative is to send these patients to a central orthopædic hospital. The former procedure has the following advantages : (1) The clinical picture of tuberculosis is made complete. This is of great importance for training purposes (for although the county sanatorium is not necessarily engaged in training students it must keep complete nursing training in the forefront). (2) It is vital to ensure the general treatment of the patient as well as the specialist treatment of the local involvement. (3) It is desirable to retain as far as possible these long-term cases where they can be most readily visited by their relatives. (4) A surprising number of orthopædic tuberculous patients are the subject of active pulmonary tuberculosis and would represent a difficult problem in an orthopædic hospital.

CHEST DISEASES.—The necessity of a liaison between a rural sub-region and regional thoracic unit has already been mentioned. In the future this will apply not only to tuberculosis but also to other chest diseases, and facilities will be provided for their medical as well as surgical treatment. The debatable point concerns the appropriate institution for the purpose. The possibilities are either special wards in the sanatorium or else in the medical wards of the general hospital. In the latter case the sanatorium physician should have access to such beds, but in practice the former method would probably be the more convenient. From what I have seen of the requirements of Dumfries

and Galloway, about one bed per 7500 of the population would be a tentative estimate of the beds *immediately* required.

TUBERCULOSIS AND FEVERS.—It is to be hoped that the new health service will separate the treatment of tuberculosis and infectious diseases. It is easy to understand how the association of these two problems began as a matter of administrative convenience many years ago. Under modern conditions their continued association is unwise, since the medical and surgical problems involved are entirely different. Tuberculosis and fevers should be treated in separate hospital units each affiliated to a central general hospital.

ADMINISTRATION.—The modern tendency to relieve hospital physicians of certain matters of day-to-day routine has much to commend it. The exact method employed to this end may, and indeed should, vary in different hospitals. Under certain circumstances, particularly where a large hospital is staffed by part-time consultants, a full-time superintendent divorced from clinical work may prove the more practicable appointment. But in a problem like tuberculosis such a division between medical and administrative work would be unsound. Sanatorium treatment is a mode of life for which a full-time physician must assume complete responsibility in all stages. Diagnosis, dietetics, heating and ventilation, special treatment, occupational treatment, and discipline must all remain firmly in his hands. The average length of stay in different sanatoria varies between six and eleven months. Thus the patient-physician relationship is quite different from that in any other type of medical work. It is most unlikely that the physician could get the best out of his hospital unless he were physician-superintendent.

In tuberculosis therefore it is to be hoped that the new service will certainly relieve the physician-superintendent of non-clinical routine, but that it will be done in the most suitable way. This would be through the appointment of a properly qualified and adequately paid steward, who would be responsible to the physician-superintendent, and would in fact be his non-medical assistant.

Rehabilitation.—The most difficult of present-day problems is rehabilitation. The question is especially troublesome in a rural area. So far as general administration is concerned the following summary is suggested, covering all forms of tuberculosis.

1. There should be an adequate basic disablement benefit payable to the patient until he is able to resume work, or until he is deemed permanently unfit for work.

2. This disablement benefit should be suitably modified to make provision for the varied needs of the family unit (*a*) whilst the patient is in hospital ; (*b*) after his discharge so long as he is unfit for work, and under the supervision of a tuberculosis physician ; (*c*) whilst he is undergoing rehabilitational training in a colony or otherwise.

3. When the patient is fit for work, but a graded return to industry is desirable, subsidised wages for part-time or sheltered work should be instituted until such time as he is pronounced fit for normal work.

4. When the patient is certified as permanently unfit for work he should receive a sickness pension.

In that scheme the medical aspects would come under the control of the tuberculosis officer or, as I have been calling him, the assistant physician. It would be he who decides to which of the categories named the patient belongs. But the actual administration of finance would be carried on by the normal local authority channels through the medical officer of health. Any alteration in the patient's category would be notified to the medical officer of health by the out-patient physician if the patient were in his own hospital authority area ; or by the medical officer of the regional rehabilitation scheme if the patient were transferred for training to the larger centre.

The *essential test of rehabilitation* is what can be done for the *chronic active case.* Quiescent or arrested cases are not such difficult problems. The Disabled Persons (Employment) Act and the Retraining Scheme of the Ministry of Labour and National Service will help those more fortunate cases but do not help the chronic active case.

For the latter the choice seems to be between colony settlement, municipal workshops or supervised homework. Which of these methods will prove the best for Scotland I do not know. It has been suggested that the Scotsman is more nostalgic in his make-up than the Englishman and is therefore less likely to make a good colonist on the Papworth model. But so far as I know neither municipal workshops affording sheltered employment, nor supervised homework have been tried in this country. Experiments in these directions will take a long time and I do not foresee any rapid development in the rehabilitation of the chronic case. The adjustment of allowances is the only development of care work by the State which can be made effective now.

SUMMARY.—Certain aspects of planning, staffing and administration of tuberculosis schemes in country districts have been discussed in light of the present knowledge of forthcoming National Health Service. The outlook for rural tuberculosis schemes under a National Health Service is good. Great flexibility of local arrangement is necessary, but a scheme under the control of a tuberculosis physician based on a sanatorium, with a central out-patient department in a general hospital, and with smaller peripheral clinics, is recommended for a predominantly rural region.

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THE VALUE OF VITAMIN A ESTIMATION IN BLOOD

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THE estimation of vitamin content in blood is usually considered a valuable aid in the understanding of vitamin metabolism. It gives also some knowledge of the vitamin saturation of the body. Since the chemical estimation of vitamin A in blood is comparatively easy it is now more frequently performed in clinical laboratories.

A number of papers have recently been published, especially in America (Popper and Steigmann), dealing with the vitamin A blood level in health and in disease. A great amount of work on vitamin A in different diseases has been done by various authors in order to assess the suitability and clinical value of this test. The questions arise : (1) What is the practical value in clinical medicine of vitamin A blood level ; and (2) what is the significance of vitamin A in blood in vitamin A metabolism ?

The values for normal vitamin A level in blood given by various authors differ somewhat, owing probably partly to modifications in the methods used, and partly to differences in nutritional standards. Vitamin A in blood is fairly constant during the day and there are comparatively slight changes on successive days. Most authors give normal values between 100 and 300 I.U. per cent. (international units), the lowest being about 70 I.U. per cent. (Lindquist). There are great individual variations of vitamin A level in normal people as shown also in our investigations. Yudkin gives the normal values of vitamin A in the range from 72 I.U. to 157 I.U. per 100 c.c., with an average of 113 I.U., and for carotene from 50 to 241 micrograms in 100 c.c. A slight sex difference in vitamin A level has been reported by some authors.

In America the vitamin A values are calculated more often in micrograms. Popper *et al.* give the normal average value of vitamin A in men as 58 micrograms in 100 c.c. plasma and 74 micrograms carotenoids, with a vitamin A carotene ratio of 0·78. In women the respective values are for vitamin A 47 micrograms in 100 c.c. plasma and 85 micrograms carotenoids with vitamin A/carotene ratio of 0·57. The variations of vitamin A in normal persons were quite extensive, ranging from 29 to 82 micrograms.

Blood vitamin A constitutes one of the stages in the general vitamin A metabolism. Other body fluids like transudates and exudates in body cavities, amniotic fluid, etc., can also contain small amounts of vitamin A as shown by us in a previous paper (*Edin.*

Med. Journ. (1945), p. 74). The aim in the present paper is to give an account of our own experience in the practical value of vitamin A estimation in blood and its comparison with vitamin A excretion in urine.

The investigations were carried out on the clinical material available in the various wards of the Royal Infirmary of Edinburgh for which we are indebted to the chiefs of these particular wards.

METHOD

Twenty c.c. of blood were withdrawn, and to prevent the coagulation a few small crystals of sodium oxalate or 2 c.c. of 3·8 per cent. sodium citrate were added. In the latter case a 10 per cent. correction of the results was made. Eight c.c. of plasma were usually obtained after the separation of red cells.

To one volume of plasma whose pH was adjusted to about five, one volume of alcohol and two volumes of petrol ether (40-60) were added and the mixture was shaken for ten minutes. The adjustment of the pH was done to secure the maximum extractability of the vitamin A and carotene which, as shown by Działoszyński, Mystkowski and Stewart, is greatest in the region of the isoelectric point of the plasma proteins. After the separation of layers another two extractions were made in the same way. The combined extracts were washed with a half volume of 3 per cent. KOH and then twice with water, dried over anhydrous Na_2SO_4, filtered and distilled down to 10 c.c. Carotene was estimated at that stage on a photoelectric colorimeter (Spekker). The petroleum ether was then evaporated to dryness, the residue dissolved in 5 c.c. chloroform and vitamin A was estimated with the Carr-Price reaction again on the photoelectric colorimeter (Dann and Evelyn, Koehn and Sherman, Kimble, Yudkin, etc.).

The application of the above method in cases of jaundice was not satisfactory as the bile pigments could not be entirely separated and interfered with the subsequent estimation of vitamin A. A modified method was therefore applied. Both methods were tried on the same sample of blood and gave the same results, within the limits of error, the second method giving slightly higher results. The modified method consisted of shaking the plasma with alcohol in an acid medium and then extracting with ethyl ether in alkaline medium. The evaporated etheral extracts were later treated similarly as in the normal method.

For examination of vitamin A in urine, 50 c.c. of urine were used. The details of the technique are published in the paper on " Vitamin A Excretion in Urine " (*Edin. Med. Journ.*, 1942, 49, 375).

RESULTS

Normal Vitamin A Level in Blood.—Before proceeding to the investigation of pathological cases we made a number of vitamin A estimations in the blood of healthy persons. As already mentioned normal blood values given by various authors differ to a certain extent. We wanted therefore to have our own values for comparison.

Altogether twelve investigations in healthy men were made. Most of them were male students of the Edinburgh Polish School of Medicine

in the age group from twenty-two to thirty years, living on normal military diet.

In our investigations the lowest value encountered in healthy persons was 72 I.U., the highest 315 I.U. per 100 c.c. of plasma, with an average of 176 I.U. per cent. The minimum carotene value found was 35 micrograms, the maximum 130 micrograms with an average of 67 micrograms per 100 c.c. of plasma.

Blood Level after Intake of One dose of Vitamin A.—To find the influence of one large dose of vitamin A on the vitamin A level in blood, 4 capsules of prepalin (total 96,000 I.U. of vitamin A) were given orally to healthy and ill people. The blood was examined before intake, and at times three, six and twenty-four hours afterwards. The results of two typical cases, one a healthy person and one in a state of convalescence after influenza, are given in Table I.

TABLE I

One Dose of Vitamin A in Healthy Persons

Time.	Subject No. 1.		Subject No. 2.	
	Carotene in μg. per cent.	Vitamin A in I.U. per cent.	Carotene in μg. per cent.	Vitamin A in I.U. per cent.
Before	129	116	137	55
3 hours	116	508	137	178
6 ,,	116	508	137	330
24 ,,	116	123	150	96

There is a very marked rise in the vitamin A level in blood after one large dose of vitamin A, the vitamin A content showing an increase of over 400 per cent. The peak occurred usually a few hours after the intake. In twenty-four hours the vitamin A returns to its normal level or just above it.

In the second case the starting value is rather lower than in healthy people due probably to the previous infection.

Blood Level after Prolonged Vitamin A Intake.—The influence of prolonged treatment with large doses of vitamin A in health and disease has also been investigated. A person living on a normal diet took 4 capsules of prepalin per day during twenty-five days (a total of 2,400,000 I.U.). Specimens of blood were always taken in the morning. The results are as shown in Table II.

The prolonged intake of large doses of vitamin A causes a marked rise in vitamin A level, the amount at the end of the experiment being nearly five times the previous value There is, however, a comparatively quick fall in the vitamin A content several days after the cessation of the treatment, to a level a little higher than at the start. The examination of urine did not reveal any traces of vitamin A during the period of treatment, which is in accordance with our previous experience (Tomaszewski).

In some pathological conditions the results of vitamin A intake differ from those described above. We investigated repeatedly a case of lymphosarcoma, which had marked skin changes consisting of dryness and pigmentation and extensive scaling. The patient had

TABLE II

Prolonged Intake of Vitamin A in a Healthy Person

Date.	Carotene in μg. per cent.	Vitamin A in I.U. [per cent.
28.1.45	96	72
7.2.45	70	178
22.2.45	451	332
13.3.45	96	130
20.3.45	112	108
10.4.45	96	110

From 28.1.45 till 22.2.45 4 capsules of prepalin (96,000 I.U.) were given daily.
Total 2,400,000 I.U. of vitamin A.

also an enlarged liver showing definite functional disturbances in laboratory tests. Examination of the blood revealed a very low blood vitamin A value 18 I.U. per cent., and vitamin A was excreted in the urine.

As there was some evidence that the lesions in the skin were due to a vitamin A deficiency, vitamin A was given in very large doses. The patient received 172,000 I.U. of vitamin A daily (100,000 intramuscularly) and 3 capsules of prepalin (72,000 I.U.), altogether about 4,000,000 I.U. in five weeks. Repeated blood examinations (see Table III) showed only a slight rise in vitamin A level. The examination of urine showed a very marked increase of vitamin A excretion during the treatment.

TABLE III

Prolonged Treatment with Vitamin A in a Case of Liver Damage

Date.	Urine.	Blood.	
	Vitamin A in I.U. per 100 c.c.	Carotene in μg. per cent.	· Vitamin A in I.U. per cent.
18.2.45	6	29	18
7.3.45	16	23	23
20.3.45	34	16	37
26.3.45	111	11	50
4.4.45	73	15	48

From 1.3.45 till 4.4.45 172,000 I.U. of vitamin A were given daily. Total about 4,000,000 I.U. of vitamin A.

The patient died and the post-mortem chemical estimation of the amount of vitamin A present in the liver revealed a high vitamin A content, the value being 1515 I.U. per gram. The total amount of vitamin A in the liver was calculated as being approximately

3,000,000 I.U. The unusual features of this case were the low blood level in the presence of a huge vitamin A store in the liver and the higher content of vitamin A in the urine than in the blood. A disturbance in the liver-blood relation must therefore be assumed.

Vitamin A Level in Liver Diseases.—The liver contains 95 per cent. of the vitamin A of the body. It is also the place of conversion of carotene into vitamin A. It is therefore understandable that liver diseases associated with parenchymatous changes and jaundice might influence vitamin A blood level. In the investigation of pathological cases we therefore directed our attention first of all to the liver cases.

Altogether 29 cases of diseases of the liver and biliary tract have been investigated. The great majority of them showed various degrees of jaundice ranging from mere traces to an icteric index of 120. The results are given in Table IV.

TABLE IV
Liver Diseases

Name.	Age.	Diagnosis.	Urine. Vitamin A in I.U. per 100 c.c.	Blood. Carotene in μg. per cent.	Blood. Vitamin A in I.U. per cent.
A. D.	30	Infective hepatitis	o	46	47
A. W.	31	,, ,,	o	30	46
P. K.	28	,, ,,	o	54	77
K. W.	24	,, ,,	...	49	49
D. R.	30	,, ,,	o	50	36
F. B.	18	,, ,,	o	44	44
T. V.	31	,, ,,	o	30	72
O. R.	30	,, ,,	o	36	14
R. K.	22	,, ,,	o	48	34
Z. N.	25	,, ,,	o	34	48
P. W.	69	Obstructive jaundice	o	39	68
A. W.	30	,, ,,	5	...	80
M. A.	42	,, ,,	o	110	41
K. H.	65	,, ,,	10	38	33
P. P.	70	,, ,,	o	36	93
A. B.	45	,, ,,	o	82	20
R. B.	42	Cirrhosis of the liver	o	25	6
A. P.	40	,, ,, ,,	o	35	59
W. T.	39	,, ,, ,,	o	152	67
M. G.	48	,, ,, ,,	o	18	44
W. B.	40	,, ,, ,,	o	96	66
N. M.	42	,, ,, ,,	o	23	41
J. J.	38	Toxic hepatitis, arsenic	23	20	103
C. K.	51	,, ,, ,,	o	55	76
T. M.	44	Toxic hepatitis	6	32	19
L. B.	73	Metastases in the liver	o	19	123
A. P.	48	,, ,, ,,	o	48	138
M. K.	38	Wilson's disease	o	28	2
W. W.	50	Weil's Disease	30	82	115

Nearly all the cases of liver diseases show a low vitamin A value in the blood. There is, however, some difference in the vitamin A level in regard to the type of liver disease. The lowest values have been obtained in cases with greatest liver damage as shown by functional liver tests.

The repeated estimations made in some cases of infective hepatitis showed a marked, progressive lowering of the vitamin A level. Similar low vitamin A values have been obtained in other cases of liver disease, although not so marked as in infective hepatitis. The results in obstructive jaundice of different origin, in cirrhosis of the liver, etc., are mostly below the normal. In two cases of neoplastic metastasis and in one case of Weil's disease the values were within the normal range. In one case of Wilson's disease only traces of vitamin A in the blood were found.'

The carotene values did not show any particular features, varying markedly and showing no direct relation to the amount of vitamin A.

Excretion of vitamin A in the urine reached quite a high level in some cases, especially in Weil's disease. In most of the cases the icteric index was estimated, but there was no direct relation between the vitamin A values and the icteric index.

Vitamin A Level in Kidney Diseases.—Vitamin A is often excreted in the urine in cases of kidney diseases ; especially in uræmic states vitamin A is always found (Tomaszewski). Owing to the loss of vitamin A in the urine, some changes in vitamin A blood level could be expected in prolonged kidney diseases. Some workers (Hedberg and Lindquist, Popper) have emphasised the very high vitamin A blood level sometimes found in kidney diseases. We investigated therefore a number of different kidney diseases. Most of them were chronic nephritis, three with nephrotic syndrome, and some cases of nephrosclerosis with high blood pressure. The results are given in Table V.

TABLE V

Kidney Diseases

Name.	Age.	Diagnosis.	Urine.	Blood.	
			Vitamin A in I.U. per 100 c.c.	Carotene in μg. per cent.	Vitamin A in I.U. per cent.
M. B.	40	Chronic nephritis	31	124	185
W. F.	41	,, ,,	20	50	36
T. B.	38	,, ,,	0	100	100
R. K.	32	,, ,,	0	82	110
W. G.	50	,, ,,	0	92	88
R. F.	28	,, ,,	0	60	85
W. M.	36	,, ,,	0	44	45
F. G.	29	Acute nephritis	0	95	220
C. B.	58	Uræmia	132	22	162
P. D.	45	,,	...	51	131
T. B.	40	,,	29	55	92
C. S.	41	,,	20	57	92
W. A.	56	,,	14	36	28
W. F.	39	Nephrosis	70	35	430
F. R.	31	,,	0	74	178
J. R.	24	Amyloid kidney	0	30	37
P. G.	40	Septic infarct of the kidney	218	48	140
J. C.	50	Nephro-sclerosis	0	60	190
B. P.	52	,,	0	69	196
E. N.	39	,,	0	106	330
N. M.	40	,,	104	36	185

Most of the kidney cases showed high normal values, and two of them values of 430 and 330 I.U. per cent. respectively. Only in four cases were there definitely low values. One of the latter was in a pre-uræmic state. The extremely high values occasionally found are in accordance with the results reported by other workers.

The results seem a little surprising in view of the loss of vitamin A in the urine which often happens in these cases (Popper). Nearly 50 per cent. of the kidney cases show vitamin A excretion in the urine, attaining sometimes considerable amounts.

Vitamin A Level in Conditioned Avitaminosis.—Fully developed clinical pictures of nutritional avitaminosis due to direct vitamin A deficiency is rare in Britain. In the clinical material of different wards one can, however, occasionally find cases of conditioned avitaminosis with marked symptoms and signs of vitamin A deficiency.

We investigated a number of cases with some clinical signs especially on the skin (hyperkeratosis, dryness, scaling) which were suspected of vitamin A deficiency owing to the underlying disease. Some authors point out that the skin changes in vitamin A deficiency are more marked in adults, while in the children the eye changes seem to be more evident. Most of our cases had for their underlying disease some grave disturbances of the intestinal absorption. Only in one case (T. G.) the cause of the avitaminosis could be traced to a real deficiency of vitamin A in the diet. Three of the patients examined complained of night-blindness. The results are given in Table VI.

TABLE VI

Conditioned Avitaminosis A

Name.	Age.	Diagnosis.	Urine.	Blood.	
			Vitamin A in I.U. per cent.	Carotene in μg. per cent.	Vitamin A in I.U. per cent.
C. W.	56	Gastrocolic fistula	0	18	9
J. B.	50	,, ,,	0	8	21
A. S.	18	Ileocolic fistula	0	14	36
T. G.	48	Nutritional deficiency	0	34	8

All the cases show very low vitamin A values, especially the case (C. W.) with gastrocolic fistula, and the above-mentioned case (T. G.).

It must be emphasised that the low vitamin A value itself is not conclusive of a clinical vitamin A deficiency. In some other cases, especially in the group of liver diseases, similar low values have also been obtained, but there were no obvious signs of avitaminosis in the skin. The best proof as to whether the skin changes are of a deficiency origin is the disappearance of the changes after extensive vitamin A treatment. In two of the cases such improvement has been found. In the two other cases the result of treatment could not be observed owing to the removal of the patients. Extensive treatment with vitamin A

has been tried in a case of ichtyosiform atrophy of the skin (Glazebrook and Tomaszewski).

Other Diseases.—A number of various other pathological conditions have been investigated for vitamin A blood values. They were cases of congestive heart failure with enlargement of the liver, diabetes, pneumonia, tuberculosis of the lung, stomach ulcer, etc. The results are given in Table VII.

TABLE VII

Various Diseases

Name.	Age.	Diagnosis.	Urine.	Blood.	
			Vitamin A in I.U. per cent.	Carotene in µg. per cent.	Vitamin A in I.U. per cent.
R. S.	63	Congestive heart failure	0	52	134
W. B.	65	,, ,, ,,	0	15	88
P. W.	30	,, ,, ,,	...	...	94
M. L.	55	,, ,, ,,	144	40	128
R. G.	46	,, ,, ,,	0	160	240
W. G.	22	Diabetes mellitus	0	99	304
W. B.	54	Stomach ulcer	0	50	136
O. J.	40	Pneumonia	157	36	78
T. G.	35	Tuberculosis of the lung	0	29	109
D. M.	32	,, ,, ,, ,,	0	76	123
M. L.	41	Steatorrhea idiopathica	4	13	33
W. W.	38	Hodgkin's disease	29	33	33

The vitamin A values are within normal range. Only in a case of idiopathic steatorrhea and one of Hodgkin's disease a low vitamin A value was found. To get normal results a proper diet must be first of all provided. The history of the cases did not reveal any vitamin A deficiency in the diet. There is a very high excretion of vitamin A in the urine in the case of pneumonia and in one case of congestive heart failure associated with enlarged liver.

DISCUSSION

The average vitamin A values in blood obtained by us in healthy people seem to be a little higher than those given by other authors. This is probably due to the fact that the persons examined were mostly young well-nourished students. The lowest values observed are in agreement with the reports of other authors.

In the experiments with the intake of a single large dose of vitamin A a quick and very marked rise of vitamin A followed. Popper *et al.* introduced this test for drawing a tolerance curve (orally 75,000 I.U. of vitamin A). The rise of the vitamin A value in cases of liver diseases was much smaller than in normal healthy persons. They attributed the flat tolerance curve in such cases chiefly to some disturbances in the intestinal absorption. The tolerance curve does not seem to be of help in defining the liver storage of vitamin A. High tolerance curves were not always parallel to the

high vitamin A content in the liver as shown by them in the biopsy specimens.

The prolonged intake of large doses of vitamin A by normal persons quickly brings a high rise in vitamin A content. After several days of treatment the fasting values are nearly five times higher than the pre-treatment figures. With the interruption of the treatment the vitamin A value falls quickly to a level which is somewhat higher than at the start. The reserve of vitamin A built up in the liver is probably responsible for the maintenance of the higher level. It must be added that a large intake of carotene does not change significantly the vitamin A values (Hoch).

The very slow rise after a large and prolonged vitamin A intake in a case of lymphosarcoma is explained by damage to the liver, which had been proved to be present by functional tests (flocculation test, hippuric acid test) and by post-mortem histological examination. There must be a marked disturbance in the release of the vitamin A from the liver into the blood. The investigation by fluorescent microscopy revealed in this case a great amount of vitamin A in the liver but there were some disturbances in the distribution of vitamin A in the liver.

The vitamin A values obtained in liver diseases such as infective hepatitis, obstructive jaundice, and cirrhosis are for the most part well below normal. In some cases extremely low values were found. As mentioned previously there was no direct relationship between the icteric index and the vitamin A level, but the duration of liver disease, especially in cases of obstructive jaundice with liver damage and in infective hepatitis, had some influence.

The decrease of vitamin A values in liver diseases develops comparatively quickly as shown by some repeated blood examinations in infective hepatitis. A marked rise, sometimes even above the average normal value, has been reported in the convalescent stage of acute hepatitis.

The low vitamin A values in liver diseases especially associated with jaundice cannot be explained only by impaired absorption in the intestine. The decrease of vitamin A values develops too quickly, often in the presence of good vitamin A reserves in the liver. Therefore besides the impairment of absorption some disturbance in the release of vitamin A from the liver into the blood must be accepted. The mobilisation of vitamin A in the liver is partly due to the sympathico-adrenal system (Young and Wald, Thiele and Guzinski).

Fluorescent microscopy shows that the absorption of vitamin A in the rat takes place in the entire small intestine, reaching the highest peak in the region between the upper and middle thirds (Popper and Volk). It starts within twenty-five minutes after feeding. Neostygmine promotes and atropine retards the absorption of vitamin A.

We must emphasise that the low vitamin A values in our liver cases given in Table IV did not reveal any direct evidence of skin

lesions. However, the low vitamin A values in blood in liver diseases can be responsible for some other symptoms of vitamin A deficiency like hemeralopia as reported by some authors (Patek and Haig, Wohl and Feldman).

The carotene values found by us in liver diseases varied over a wide range. The average value of carotene was lower than in normal persons. Some authors report a decrease of the vitamin A/carotene ratio in liver diseases. This is probably due not so much to disordered conversion of carotene to vitamin A, but to the lowering of vitamin A values. A detailed study on vitamin A content in liver was made in Britain by Moore and in Holland by Wolff.

The vitamin A values in renal diseases are in the great majority of cases within the normal range. Some cases show even a very high vitamin A value. As mentioned previously one would expect rather a low vitamin A level owing to the excretion of vitamin A in urine. The excretion in urine can be sometimes very high as shown in the tables. In the case of treatment with large doses of vitamin A (Table III) we found on repeated examinations actually higher vitamin A values in the urine than in the blood. Another such example is given in Table V, case P. G. No proper explanation can be given for this fact at present. In cases of kidney diseases vitamin A has been found by the aid of fluorescent microscopy in the renal parenchyma (Popper).

In cases of conditioned avitaminosis with marked clinical signs the causes of it are evident. It is known that the vitamin A level in blood depends on several factors such as nutritional intake, impairment of intestinal absorption, increased demand and utilisation and, finally, the disturbances in interaction of liver and blood.

We must again emphasise that the low vitamin A blood values are not always associated with definite skin lesions typical for vitamin A deficiency. However, early symptoms like night-blindness can be more often found. Three of our patients in the group of conditioned avitaminosis complained of this trouble. To have definite evidence a dark adaptation test ought to be performed in suspected cases. However, besides vitamin A, some other factors can be responsible for impaired dark adaptation (Stewart).

The results obtained in various other diseases are not significantly abnormal. In those cases there was no deficiency of vitamin A in the diet. The normal results would be therefore understandable. We have investigated only a limited number of such cases, but low values have been reported in some infections (pneumonia), anæmia, gastrointestinal carcinoma, etc. (Popper et al.). Of our cases only two showed a definite low vitamin A value. One of them was a patient with idiopathic steatorrhea, the other had Hodgkin's disease associated with impairment of the liver function. In the latter case an ichtyosiform atrophy of the skin was present ; however, it did not change markedly after extensive vitamin A treatment.

A few words should be said about the excretion of vitamin A in urine. As shown in the tables, vitamin A is excreted in a number of cases. This excretion is associated with different pathological states, such as kidney disease, liver disease, infective disease connected with high temperature, neoplasms, and some other disorders.

The mechanism of this excretion is not well known. Since vitamin A exists in plasma in the form of a water soluble complex with a plasma protein, probable serum albumin (Działoszyński, Mystkowski and Stewart), it might be expected that it is carried out as such into the urine in cases of altered permeability of the capillaries in the glomeruli tuft. Lawrie, Moore and Rajagopal found that vitamin A in urine was not always accompanied by a protein—not necessarily heat-coagulable. According to Bing very high doses of vitamin A produce in dogs a significant rise in the tubular excretory mass and a moderate increase in renal plasma flow and filtration rate.

SUMMARY

Investigations have been made of the vitamin A content of blood and urine in healthy and ill persons.

The vitamin A level in the blood of 12 healthy males has been found to lie between 72 and 315 I.U. per 100 c.c. of plasma, the average being 176 I.U. per cent. The normal carotene values were found between 35 and 130 micrograms with an average of 67 micrograms per cent.

One large dose of vitamin A of 96,000 I.U. taken orally gives in a healthy person a quick rise of vitamin A in the blood amounting to 400 to 500 per cent., reaching the maximum a few hours after the intake.

Prolonged intake of large doses of vitamin A gives a marked rise of vitamin A in blood in healthy persons with a comparatively quick fall after interruption of the intake.

Prolonged treatment with very large doses of vitamin A in cases of liver damage gives a much smaller and slower rise of vitamin A in blood with a large amount of vitamin A stored in the liver.

Low vitamin A values independent of the intake of vitamin A in the diet can be found in various diseases. In cases such as infective hepatitis, obstructive jaundice, cirrhosis of the liver, low vitamin A content has been found. Vitamin A estimation has some diagnostic and prognostic value in such cases. No marked changes in vitamin A values have been found in the renal diseases. In some renal cases extremely high vitamin A values have been noticed.

Low vitamin A values have been found in diseases which cause conditioned avitaminosis with clinical signs of vitamin A deficiency. Low vitamin A values are not always associated with definite clinical signs of avitaminosis.

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THE EFFECT OF ARTERIOVENOUS ANEURYSMS ON BLOOD VOLUME AND BLOOD PICTURE

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THE changes occurring in the cardiovascular system as a result of arteriovenous aneurysms are complicated, and the mechanism of their production is as yet uncertain. Holman (1923) considered that an increase in blood volume was an important sequel of such communications. He suggested that the decrease in peripheral resistance in the part of the circulation containing the fistula was compensated by an increase in the amount of blood available to be pumped through this part, the increased volume being accommodated in dilated arteries and veins proximal to the communication. Direct evidence of an increase in blood volume was not obtained in the single case he then investigated, but later (1924 *a, b*) he found an increase in the blood volume of dogs with experimental fistulæ, the increase being proportional to the size of the communication. He considered that the fall in pulse rate (Branham phenomenon) and rise in blood pressure which have been shown to occur on closure of a fistula, were due to the decrease in venous filling when the increased volume was returned to its original channels. In 1937 he reviewed the whole problem and reported a decrease in blood volume in two cases of acquired fistula and one of congenital fistula, after operation. These conclusions have been criticised, particularly by Lewis and Drury (1923), who considered that the loss of peripheral resistance in one part of the circulation could be compensated by alterations in vascular tone elsewhere, and that the changes in pulse rate and blood pressure were due to alterations in arterial and not in venous pressures. Until recently there have not been many opportunities for further investigation. Rowntree *et al.* (1929) found large blood volumes in four cases with traumatic arteriovenous aneurysms and normal blood volumes in three cases with congenital arteriovenous aneurysms. A fall in volume occurred in four of these cases when the vessels were ligated or an extremity amputated. Ellis and Weiss (1930) found a normal blood volume in one untreated case of arteriovenous aneurysm, and Kennedy and Burwell (1937) found a reduction in volume after closure of an arteriovenous fistula.

At Professor J. R. Learmonth's suggestion we estimated the blood volume in 15 cases of traumatic arteriovenous aneurysm under his care in a Scottish E.M.S. Hospital, and have been able to compare the results obtained with the other cardiovascular manifestations recorded by his staff.

The blood volumes were estimated by the dye method, using Evans blue (T-1824) and the technique described by Davis (1942); with the patient in the recumbent position, 12 mg. of dye in 5 ml. of normal saline was injected into an arm vein, and ten minutes later blood was removed from a vein in the other arm. The dye concentration in the serum was estimated with a " Spekker " photo-electric absorptiometer, by comparison with a standard solution made up with serum obtained before injection of dye. From this the plasma volume was calculated. A further 3 ml. of blood was collected in a Wintrobe tube and on this hæmoglobin (Haldane), red blood cell count and hæmatocrit determinations were made. From the plasma volume and hæmatocrit values the blood volume was calculated, and from the blood volume and hæmoglobin level was obtained the total hæmoglobin mass, 100 per cent. on the Haldane scale being taken as 13·8 g. of hæmoglobin per 100 ml.

The 15 patients were investigated before operation and four to ten weeks after successful occlusion of their fistulæ. The position of the fistulæ and their duration are given in Table I. The blood volumes, blood hæmoglobin

TABLE I

Site and Duration of Injury in 15 Cases of Arteriovenous Aneurysm

Case.	Communication between		Interval in weeks.	
	Artery.	Vein.	Injury to First Test.	Operation to Second Test.
1*	Common carotid	Internal jugular	40	8
2	Internal carotid	Internal jugular	19	4
3	Axillary	Axillary	27	9
4	Axillary	Axillary	12	10
5	Axillary	Axillary	12	9
6	Brachial	Basilic	13	6
7	Brachial	Basilic	46	9
8	Profunda	Femoral	(1) 30 (2) 43	6
9*	Profunda	Femoral	48	8
10	Medial circumflex	Medial circumflex	9	10
11*	Medial circumflex	Medial circumflex	17	5
12	Popliteal	Popliteal	21	6
13	Popliteal	Popliteal	16	(1) 4 (2) 7
14	Popliteal	Popliteal	11	6
15	Posterior tibial	Posterior tibial	23	6

* Transfused at operation.

levels and total amounts of hæmoglobin, before and after operation, are shown in Table II. The results may be considered from two aspects, first, whether the initial values were high, and secondly, whether there was a change in the values after closure of the fistulæ.

Pre-operative Values.—In considering the pre-operative values it was necessary to make allowance for variations in the body size of the subjects. This was done by calculating the blood volume and total hæmoglobin per square metre of body surface. The surface area was chosen as the criterion of body size, since it appears from

the results of Rowntree *et al.* (1929), Gibson and Evans (1937) and Davis (1942), that in normal men a closer correlation exists between this measurement and the blood volume than between body weight and blood volume. The figures for blood volume and total hæmoglobin

TABLE II.

Blood Volume, Hæmoglobin Percentage and Total Hæmoglobin before and after Operation, in 15 Cases of Arteriovenous Aneurysm

Case.	Surface Area sq. m.	Blood Volume, ml.			Hb per cent.			Total Hb, g.		
		Pre-operative.	Post-operative.	Change.	Pre-operative.	Post-operative.	Change.	Pre-operative.	Post-operative.	Change.
1	1·88	5700	5550	− 150	122	104	−18	965	795	−170
2	1·61	4400	3850	− 550	98	94	− 4	595	500	− 95
3	1·765	5100	5200	+ 100	116	116	0	815	825	+ 10
4	1·52	4100	4000	− 100	112	104	− 6	635	575	− 60
5	1·72	5500	5000	− 500	106	104	− 2	805	710	− 95
6	2·075	6100	5500	− 600	100	96	− 4	845	735	−110
7	1·72	5800	5000	− 800	100	94	− 6	795	645	−150
8	2·00	(5500)	...	...	(110)	...	...	(830)	...	...
		6800	5300	1500	110	108	− 2	1040	780	−260
9	1·945	5300	5400	+ 110	106	100	− 6	780	745	− 35
10	1·905	6500	5700	− 800	100	102	+ 2	890	805	− 85
11	1·78	5100	4900	− 200	114	106	− 8	805	715	− 90
12	1·785	5200	4900	− 300	106	100	− 6	755	670	− 85
13	1·90	...	(6700)	(+ 600)	...	(110)	(+ 6)	...	(1020)	(+145)
		6100	5600	− 500	104	96	− 8	875	745	−130
14	1·95	6100	5800	− 300	120	104	−16	1010	830	−180
15	1·61	4800	5100	+ 300	112	100	−12	740	700	− 40

per square metre are not shown individually, but the mean values, together with the mean hæmoglobin percentages, are shown in Table III. For comparison, the mean blood volume of eighteen normal men is given, these being the 11 cases reported by Davis (1942) together with a further seven since investigated by us.

The mean blood volume per square metre was slightly higher in the patients with patent fistulæ (3030 ml.) than in the normal men (2910 ml.), but this difference was slight, and when the individual figures were considered it was clear that in no case could the pre-operative values be considered to be abnormally high ; the highest concentration of blood in a patient with a patent fistula was 3400 ml./sq. m., and two normal men had concentrations of 3200 ml./sq. m. This difference is within the limits of experimental error. Case 8 was investigated twice before operation. Thirty weeks after the injury the blood volume was 2750 ml./sq. m., thirteen weeks later it was 3400 ml./sq. m., which suggests that definitely abnormal blood volumes might develop if the aneurysms remained patent for longer periods.

The mean pre-operative hæmoglobin level in the blood was 108·4 per cent., which was high. The value of 452 g./sq. m. for total hæmoglobin was also probably higher than normal, but figures for normal men are not available for comparison.

Post-operative Changes.—It will be seen that the post-operative blood volume was lower than the pre-operative in 12 of the 15 cases. There was a decrease of less than 500 ml. after operation in five cases and of 500-1500 ml. in the remaining seven. There was no apparent relation between the presence or absence of a decrease, or its magnitude, and the time that had passed since operation. It appears, however, that the decrease may not occur immediately after closure. Case 13, when investigated four weeks after operation, had a higher blood volume than before, but by the seventh week the blood volume was less than before operation.

In 13 cases there was a fall in the blood hæmoglobin level after operation, 10 cases falling by 2-8 per cent. Hb, and 3 by 12-18 per cent. Hb. The other 2 cases showed no appreciable change. With

TABLE III

Mean Blood Volume, Hæmoglobin Percentage and Total Hæmoglobin in 15 Cases of Arteriovenous Aneurysm, before and after Operation. The Blood Volumes are compared with those of 18 Normal Men.

	Normal Men (18).	Cases with Arteriovenous Aneurysms (15).		
		Pre-operative.	Post-operative.	Mean Difference.
Blood volume, ml./sq. m.	2910	3030	2820	211
Standard dev.	*267*	*256*	*188*	*239*
t				*3·42*
Hb per cent.		108·4	101·8	6·5
Standard dev.		*4·95*	*6·1*	*5·53*
t				*4·59*
Hb, g./sq. m.		452	397	55·3
Standard dev.		*42·5*	*37·6*	*32·25*
t				*6·64*

When *n* = 15 the mean difference is significant if *t* = 2·145 or more.

this fall in hæmoglobin level there was a parallel fall in the red blood cell count, so that there was no significant change in the colour index, which was never below 0·92 and in 7 cases was actually higher after operation than before. These data suggest that the fall in hæmoglobin was not due to loss of blood at the time of operation. In only 3 cases had hæmorrhage been sufficient to require transfusion (see Table I), and it would appear that by the time of the post-operative investigation any loss at operation had been replaced.

There was a marked post-operative fall in the total hæmoglobin. In only 1 case was there no reduction ; 8 cases showed a fall of 35-95 g. and 6 a fall of 110-260 g.

In Table III it is shown that the mean fall in blood volume per square metre for the 15 cases was 211 ml., whereas the mean fall in blood hæmoglobin level was 6·5 per cent. Hb and the mean fall in hæmoglobin mass per square metre was 55·3 g. Statistical analysis of these changes showed that they were too large to be due to chance.

DISCUSSION

The data showed that the presence of a direct communication between the arterial and venous systems tended to produce an increase in blood volume, but that this increase was not constant. The increases which were observed were very variable in amount, as might be expected when it is realised that the circulatory changes are dependent on many factors. These probably include the duration of the condition, the distance of the communication from the heart, the calibre of the vessels involved and the size of the opening. No correlation could be found between any of these factors and the changes in blood volume observed but in so few cases this is not surprising.

The changes in blood volume were compared with other circulatory changes. In some cases radiological measurement of the heart before and after operation had been carried out ; the changes in diameter and area could not be correlated with changes in blood volume. The two circulatory phenomena associated with fistulæ, namely, slowing of the pulse and rise of blood pressure on occlusion of the communication, did not appear to be related to the presence of an increased blood volume. There were cases with a negative Branham phenomenon among those with the most markedly increased blood volume, and others with positive Branham tests among those with no apparent increase in blood volume.

The inconstancy of the rise in blood volume after the establishment of an arteriovenous aneurysm, and the occurrence of alterations in the heart size, pulse rate and blood pressure, independent of alterations in blood volume, suggest that it cannot be the important essential change that Holman (1923 ; 1924 *a*, *b*) postulated. It is true that in the present cases the fistulæ had not been present for long and that greater and more constant changes in volume might have been present after a longer period ; but the communications had been present for a sufficient length of time for other circulatory changes to occur.

Increase in total hæmoglobin in the presence of a fistula was of more constant occurrence. When the blood volume was high this was not always apparent from the blood hæmoglobin level, as the extra volume carried more hæmoglobin at normal levels, but when the blood volume was normal it was apparent and produced a mild polycythæmia. This increase in the circulating hæmoglobin can be explained as an effort to compensate the reduced flow of oxygenated blood to all parts of the body ; Lewis and Drury (1923) considered that in some cases the flow might be only 50 per cent. of normal.

SUMMARY

1. The blood volume was estimated in 15 cases with patent traumatic arteriovenous aneurysms and again after occlusion of the communications.

2. While the volumes found before operation were not high enough to be definitely abnormal, a post-operative fall in volume occurred in 12 of the cases, suggesting that the presence of a fistula tended to produce an increased volume.

3. No reason for the inconstancy of the increase could be found, and certain circulatory changes were present independent of any increase of blood volume, suggesting that an increase is not such an important result of a communication as has been thought.

4. The total circulating hæmoglobin was considerably increased in the presence of a fistula. In some cases this was apparent from the blood picture, which showed a mild polycythæmia.

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NOTES

A QUARTERLY Meeting of the College was held on Tuesday, 16th July, the
President, Dr D. M. Lyon, in the Chair. The President
Royal College of intimated that Major-General Sir Alexander Gordon
Physicians Biggam, K.B.E., C.B., M.D. EDIN., F.R.C.P. LOND., Sir
of Edinburgh. Henry Hallet Dale, O.M., G.B.E., M.D. CAMB., F.R.C.P.
LOND., Neil Hamilton Fairley, C.B.E., M.D. MELB., F.R.C.P. LOND., Sir
Alexander Fleming, M.B. LOND., F.R.C.P. LOND., Sir John Fraser, BART.,
K.C.V.O., M.C., M.D., F.R.C.S. EDIN., The Rt. Hon. Lord Moran, M.C., M.D.
LOND., P.R.C.P. LOND., and Major-General Sir Percy Stanley Tomlinson,
K.B.E., C.B., D.S.O., F.R.C.P. LOND., had accepted the Honorary Fellowship
of the College. Dr Ronald Haxton Girdwood (Edinburgh), Dr Angus Henry
Campbell (Redhill, Surrey), and Dr Stanley Galbraith Graham (Glasgow)
were introduced and took their seats as Fellows of the College. Major William
Happer, I.M.S., Dr Robert James Kellar, M.B.E. (Edinburgh), Dr Gordon
Douglas Malcolm (Bridge of Earn, Perthshire), and Sir Andrew Davidson
(Edinburgh) were elected Fellows of the College.

AT a Graduation Ceremonial held in the McEwan Hall on Wednesday,
24th July 1946, the following degrees were conferred :—
University of *The Degree of Doctor of Medicine :*—Ahmed El
Edinburgh. Shahed, Egypt, M.B., CH.B., 1937. Some Observations
on Spanner's Conception of the Placental Vascular Arrangement and the
Maternal Blood Circulation through it. (*In absentiâ*) ; James Innes, Scotland,
M.B., CH.B. (with Honours), 1937. Studies in Malaria Chemotherapy (*Highly
Commended for Thesis*) ; Robert James Gerard Rattrie, Scotland, M.B., CH.B.,
1943. An Assessment of Clinical Jaundice occurring in a Venereal Diseases
Clinic (*Commended for Thesis*) ; James Scott Robson, Scotland, M.B., CH.B.
(with Honours), 1945. Fluid Retention in Patients with Chronic Liver
Disease (*Commended for Thesis*) (*In absentiâ*) ; David Crombie Ross,
Scotland, M.B., CH.B., 1937. Vitamin C in Tuberculosis : Its Metabolism
and Therapeutic Value ; Ian Duncan Willatt, England, M.B., CH.B., 1939.
The Effects of Amœbic Dysentery as encountered in British Troops from
1942 to 1946 (*Commended for Thesis*) (*In absentiâ*).
The Degree of Master of Surgery :—Ian Scott Smillie, O.B.E., Scotland,
M.B., CH.B., 1931. Injuries of the Knee Joint (*Awarded Gold Medal for
Thesis*) ; Robert Strang, England, M.B., CH.B., 1925. Abdominal Surgery
at a Field Surgical Unit.
The Degrees of Bachelor of Medicine and Bachelor of Surgery :—Grace
Barker, B.A. (OXON), England ; Patricia Mary Barraclough, England ;
Elizabeth Lawler Batchelor, Canada ; Margaret Rycroft Bate, B.A. (LOND.),
England ; Francis Alexander Beale, Scotland ; Fiona Melville Bennett,
Scotland ; Hugh Lawson Binnie, Scotland ; William Logan Blackett,
Scotland ; William John Oldfield Box, England ; Mary Mackay Macdonald
Boyd, M.SC. (N.Z.), PH.D. (LOND.), New Zealand (with Honours) ; Egan
Rupert Brooks, Jamaica ; John Richard Brotherton, England ; Joseph Brown,
Scotland ; Pamela Jane Brown (*née* Rickword), England ; Stanley Parker
Bruce, Scotland ; Mary Craig Buchanan, Scotland ; Katharine Anne Burn-
Murdoch, Scotland ; James Burton, Scotland ; Alick Cameron, England ;
Walter Wilson Campbell, Scotland ; Ian Walker Clark, Scotland ; Barbara
Evelyn Clayton, England (with Honours) ; Douglas Clement Cockburn, B.A.
(CANTAB), Scotland ; Iole L'Estrange Kilburn de Lingen, England ; Andrew
Cairns Douglas, Scotland ; David Duncan, Scotland ; John Alexander Ewing,
Scotland ; Robert Marius Foster, Scotland ; Angus David Beattie Fothering-

ham, England; Robert Frater, Scotland; Edwin Norman Sargood Fry, England; Kenneth Gordon Gadd, England; William Ritchie Galloway, Scotland; Constance Adelaide Gibbs (*née* Mitchell), England; Robert Angus Fletcher Gilbert, Scotland; James Murray Gill, England; Roy Gillott, England; Philippa Ann Glyn, England; Abraham Goldberg, Scotland; Richard Herbert Gosling, Scotland; Jessie Ellen Joyce Grainger, Scotland; Eric Robert Gunn, Scotland; Sheila Inglis Haldane, Scotland; Kenneth Charles Robertson Halliday, Scotland; Theodore Lindsay Henderson, Scotland; John Stuart Holden, England; Ronald Houston, Scotland; Moira Baskerville Hughes, Scotland; Elizabeth Stewart Humble, Scotland; Richard Cenric Humphreys, Wales; Morag Lillie Insley (*née* Henderson), Scotland; Andrew Scott Ireland, Scotland; Gordon Irvine, Scotland; Allan Boyd Jamieson, Scotland; David Anthony Llewellyn Jones, Wales; James Douglas Kerr, Scotland; Alison Bertha King, England; Isabella Kingan, Scotland; Charlotte Marjorie Methven Kirkcaldie, Scotland; Ian Cunningham Sinclair Knight, Australia; Rodney Russell Lam, China; Samuel George Edward Laverty, B.SC., England; Rosemary Whitehead Lawrence, England; Isabel Joan Kirkwood Ledger, England; Mary Kate Lethem, England; Ian Calder Lewis, Australia; Kok Ann Lim, B.SC., Straits Settlements; Peter Deans Livingstone, Scotland; Helenor Ferguson Lochhead, Scotland; John Alexander Loraine, Scotland (with Honours); Ethel Margaret Joan Loudon, Scotland; Allan Colin McDougall, Scotland; Margaret Munro MacDougall, Scotland; William Aitken Macdougall, Scotland; Patrick Cushny MacGillivray, England; Ronald Charles MacGillivray, Scotland; Donald Melvin MacKay, Scotland; Ian Grant MacKenzie, Scotland; David Livingston MacKinnon, Scotland; John MacLean, Scotland; Alastair McNab, Scotland; Robert Cunningham Macnair, Scotland; Betty Mallace, Scotland; Dilys Manners, England; Thomas Swinton Martin, Scotland; Kenneth William Matheson, B.SC., Scotland; Katherine-Alice Mercer, England; John David Craig Millar, Scotland; Francis Robert Duncan Minett, England; Robert Richard Weir Mirrey, Scotland; Irene Mary Josephine Monaghan, Scotland; Isobel Stewart Mowat, Scotland; Elspeth Margaret Orr, Scotland; Owen Elias Owen, Wales; John Richard Page, England; Herbert Murray Park, England; Frank Lionel Rawson, England; Alexander Reid, Scotland; David Reid, Scotland; Myrtle Vivien Richards, England; Boris Ruebner, Czecho-Slovakia; William Roy St Clair, Scotland (with Honours); Kathleen Isobel Scott, Scotland; Anne Kathleen Irvin Sellers, England; William Lawson Sewell, Scotland; Helen Margaret Shearer (*née* Lenman), Scotland; Charles Gordon Sim, Scotland; David Alexander Sime, England; Donald Charles Simpson, England; Kenneth Sinclair, Scotland; George McMillan Smibert, Scotland; Leslie Stewart Smith, Scotland; Ian Ferguson Sommerville, Scotland; Alan Robert Somner, Scotland; John Oliver Taubman, Scotland; Emily Dorothy Jean Todd, Scotland; Colin Heriot Macdonald Walker, Scotland; Charles Henry Wheatley, England; Rachel Brodie White, Scotland (with Honours); John William Whittick, B.SC., Scotland; Abraham Jose Williams, Nigeria; Cyril Eddy Williams, England; Allen Templeton Wilson, Scotland; James Thomson Wright, Scotland; Duncan Yuille, England; Monica Margaret Zealley, England.

Diploma in Psychiatry :—James Black Methven, M.B., CH.B. (*In absentiâ*).

Diploma in Tropical Medicine and Hygiene :—William Bain, M.B., CH.B. (GLASG.); Joseph Antoine Philippe Bouton, M.B., CH.B. (*In absentiâ*); George Buchanan, L.R.C.P. (ED.), L.R.C.S. (ED.), L.R.F.P. AND S. (GLASG.) (*In*

absentiâ) ; Christian William Fraser MacKay, M.B., CH.B. (GLASG.) ;
Jagdish Prasad Mehrotra, M.B., B.S. (PATNA) ; Kenneth Desmond Moynagh,
M.R.C.S. (ENG.), L.R.C.P. (LOND.) ; William Oliver Petrie, M.B., CH.B. (*In absentiâ*) ; John Morrison Smith, M.B., CH.B. (GLASG.)

The Polish School of Medicine at Edinburgh—The Degree of Doctor of Medicine :—Kazimierz Durkacz, M.B., CH.B. *Thesis*—" The Congenital Absence of Teeth with Special Reference to Traumatic Anodontia " ; Lukasz Kulczycki, M.B., CH.B. *Thesis*—" Acrodynia in Childhood " ; Magdalena Krystyna Munk, M.B., CH.B. *Thesis*—" The Influence of a Vitamin E deficient Diet on the Testes of Mice " ; Roman Rejthar, M.B., CH.B. (POZNAN). *Thesis*— " Synovial Sarcoma " ; Olgierd Rymaszewski, M.B., CH.B. *Thesis*—" The Changes in the Suprarenal Glands of Mice in Connection with Vitamin E " ; Tadeusz Józef Szczesniak, M.B., CH.B. *Thesis*—" The Changes in Mouse Liver caused by prolonged Vitamin E Deficient, or Vitamin E Rich, Diets " ; Henryk Wójcicki, M.B., CH.B. *Thesis*—" The Therapy of Psychoneurosis by Narco-Analysis."

The Degrees of Bachelor of Medicine and Bachelor of Surgery :—Antoni Bobak, Wladyslaw Gałecki, Karol Getta, Zenon Giedrys, Eliasz Grubsztejn, Wojciech Kaczmarek, Andrzej Kurowski, Tadeusz Łabęcki (*In absentiâ*), Zbigniew Liskowicz, Zbigniew Milewski, Liwia Mitis, Karol Sztabert (*In absentiâ*), Leon Wachała, Adam Wloczewski.

Faculty of Medicine : Awards of Scholarships, Bursaries, Prizes, etc. : The Cameron Prize in Practical Therapeutics—Albert Szent-Györgyi, M.D., PH.D. (CANTAB), Professor of Medical and Organic Chemistry in the University of Szeged, Hungary, in recognition of his distinguished contributions to our knowledge of Vitamin C. *Thesis Gold Medallist*—Ian Scott Smillie, O.B.E., CH.M. *The Ettles Scholarship and Leslie Medal*—Rachel Brodie White, M.B., CH.B. ; *The Scottish Association for Medical Education of Women Prize* —Rachel Brodie White, M.B., CH.B. *The Chiene Medal in Surgery*—Ian Scott Smillie, O.B.E., CH.M. *The Mouat Scholarship in the Practice of Physic*— John Alexander Loraine, M.B., CH.B. *The Stark Scholarship in Clinical Medicine*—Ronald Foote Robertson, M.B., CH.B. *The Buchanan Scholarship in Midwifery and Gynæcology*—Mary Mackay Macdonald Boyd, M.SC., PH.D., M.B., CH.B. *The James Scott Scholarship in Midwifery and Gynæcology*— Ronald Charles MacGillivray, M.B., CH.B. *The Vans Dunlop Scholarship in Materia Medica and Medicine*—John Alexander Loraine, M.B., CH.B. *The Vans Dunlop Scholarship in Pathology and Surgery*—Hugh Arnold Freeman Dudley. *The Dorothy Gilfillan Memorial Prize*—Barbara Evelyn Clayton, M.B., CH.B. *The Beauey Prize in Anatomy and Surgery*—William Roy St Clair, M.B., CH.B. *The Keith Memorial Prize in Systematic Surgery*— Ian Ferguson Sommerville, M.B., CH.B. *The Annandale Medal in Clinical Surgery*—Barbara Evelyn Clayton, M.B., CH.B. *The Murdoch Brown Medal in Clinical Medicine*—Allan Colin McDougall, M.B., CH.B. *The Royal Victoria Hospital Tuberculosis Trust Medal*—John Alexander Loraine, M.B., CH.B. *The Thomson Memorial Medal in Child Life and Health*—John Alexander Loraine, M.B., CH.B. *The Wightman Prize in Clinical Medicine*—Andrew Cairns Douglas, M.B., CH.B. *The Pattison Prize in Clinical Surgery*—Ian Ferguson Sommerville, M.B., CH.B. *The Lawson Gifford Prize in Obstetrics and Gynæcology*—Barbara Evelyn Clayton, M.B., CH.B. *The Maclagan Prize in Forensic Medicine*—Eileen Vanora McWilliam, B.SC. *The Stirton Bursary*—Margaret Stirling. *The Colonel Thomas Biggam Memorial Medal and Prize in Pathology*—Rosemary Helen Macnaughton Davie. *The Lewis Cameron Undergraduate Prize in Bacteriology*—Donald Stewart McLaren.

The Cunningham Memorial Medal and Prize in Anatomy—Walter Frederick Coulson. *The Senior John Aitken Carlyle Bursary in Anatomy and Physiology* —Walter Frederick Coulson. *The Junior John Aitken Carlyle Bursary in Anatomy and Chemistry*—Michael Robert King. *The Mackenzie Bursaries in Anatomy*—Jean Morag Arkieson, Michael Robert King, Gerald Francis Morris Russell, Alan William McIntosh Smith. *The Ian Oswald Prizes in Anatomy*—Margaret Kennedy, Robert Kilpatrick. *The Whiteside Bruce Bursary*—Anne Templeton Lambie, Gerald Francis Morris Russell (equal). *The Vans Dunlop Prize in Botany and Zoology*—Anne Templeton Lambie. *The Vans Dunlop Prize in Physics and Chemistry*—Anne Templeton Lambie.

The Address to the new Graduates was delivered by the Promotor, Professor G. F. Marrian, D.SC., F.R.S.

AT a meeting of the Royal College of Surgeons of Edinburgh held on 25th July,

Royal College of Surgeons of Edinburgh. Mr James M. Graham, President, in the Chair, the following who passed the requisite examinations were admitted Fellows : Robert David Irving Beggs, M.B., B.CH. UNIV. CAMB. 1938 ; Herbert William Gallagher, M.B., B.CH., B.A.O. Queen's University, Belfast, 1939 ; Gavin Chapman Gordon, M.B., CH.B. UNIV. GLASG. 1934 ; David Bernard Handelman, L.R.C.P. AND S. EDIN. (Triple) 1940 ; Ronald William Barrington Holland, M.B., C.H.B. UNIV. EDIN. 1937 ; Charles McTaggart Hopkins, M.B., B.S. UNIV. MELB. 1934, M.R.C.O.G. LOND. 1939 ; Philip Jardine, L.R.C.P. AND S. EDIN. (Triple) 1939 ; Jeremiah Patrick Lane, M.B., B.CH. UNIV. COLLEGE, CORK, 1937 ; Thomas John McCormac, M.B., CH.B. UNIV. NEW ZEALAND 1938 ; Matthew McLearie, M.B., CH.B. UNIV. GLASG. 1938 ; Archibald McLaren Millar, M.B., B.S. UNIV. MELB. 1936 ; George Herbert Moore, M.B., CH.B. UNIV. MANCH. 1934 ; John Francis Paxton, M.B., B.CH. UNIV. CAMB. 1940 ; Herbert Hillary Pearson, M.B., B.S., UNIV. SYDNEY 1938 ; Norman Arthur Punt, M.R.C.S. ENG., L.R.C.P. LOND. 1942 ; Sidney Sacks, M.B., CH.B. UNIV. CAPE TOWN 1937 ; Derek C Simpson, M.B., CH.B. UNIV. NEW ZEALAND 1940 ; William Maurice Essen, M.R.C.S. ENG., L.R.C.P. LOND. 1936.

Higher Dental Diplomates :—The following candidates, having passed the requisite examinations, were admitted Higher Dental Diplomates : John Wylie Cunningham, L.D.S., R.F.P. AND S. GLASG. 1938 ; George Alexander Cuthbertson, L.D.S., R.F.P. AND S. GLASG. 1939 ; Evan Wynn Davies, L.D.S. UNIV. LIVERPOOL 1940 ; George Alexander Lammie, L.D.S., R.C.S. EDIN. 1943 ; Donald Verner Taylor, L.D.S., R.C.S. ENG. 1930.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and

Triple Qualification Board. the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG. :—Edward Allen Barrett, William Rhind Brown, William Sinclair Brown, Mary Gray Buchanan, John Duncan, Angus Sinclair Dunn, Margaret Webster Gerrard, Robert Floyd Gray, Ian Lamond, George Arthur Lawrenson, Julia Isabel Leitch, Graeme Clifford Mackie, Catherine Helen Mair, Hamish Morrison Mann, Jeannette Bethel Morrison, Nathan Abraham Oppenheim, Alan Charteris Pole, John Lamptey Quartey-VanderPuije, John Nestor Rankin, Bernard William Thomas Richardson, Harry Kaye Rose, Agnes Whyte Muir Scott, Kirsty Florence Semple, William Pow Thomson, John Watson, Abraham Jose Williams.

THE SENSITIVITY OF BACTERIA TO THE ACTION OF PENICILLIN

By J. P. DUGUID, M.B., B.Sc.

From the Department of Bacteriology, Edinburgh University

INTRODUCTION

THE clinical use of penicillin in the treatment of infections is determined by the sensitivity of the causal organisms. It has been customary to distinguish bacteria as being either " penicillin sensitive " or " penicillin resistant." On the basis of some *in vitro* test, such as the " agar plate and gutter test," an organism is found to be " sensitive " or " resistant " according to whether or not its growth is inhibited by penicillin in a concentration of about 0·1 to 0·3 units per ml. This distinction is in many respects a useful one, for during systemic administration at normal dosage rates (*e.g.* 100,000 to 200,000 units per day) the penicillin content of the blood serum and of infective exudates is commonly .bout 0·05 to 0·1 units per ml. and is seldom greater than 0·3 units Si · ml. (McAdam *et al.*, 1944 and 1945). It is possible, however, Jo obtain much higher concentrations of penicillin in the body fluids ; *M·* example, up to a few units per ml. in the serum during systemic *in*ministration at high dosage rates, from 10 to 500 units per ml. in ₘe urine during systemic administration at normal dosage rates, and ;p to 10, 100 or 1000 units per ml. in the cerebrospinal fluid and in ·erous cavity, abscess cavity and wound exudates, when penicillin is .ntroduced locally. Many of the organisms normally considered " penicillin resistant " are fully susceptible to these higher concentrations of penicillin ; for example, Strept. fæcalis (Helmholz and Sung, 1944 *a* and *b*), some Brucella strains (T'ung, 1944), and some of the Gram-negative bacilli (Thomas and Levine, 1945). The possibility is thus suggested that, in suitable cases, infections with these " resistant " organisms may respond to penicillin treatment.

Quantitative sensitivity measurements for *a number of strains of the same species* have been recorded by several authors : for Staph. aureus, by Rammelkamp and Maxon (1942), Spink, Ferris and Vivino (1944) and Plough (1945) ; for various streptococcal species, by Watson (1944) and Dawson, Hobby and Lipman (1944) ; for the gonococcus, by Cohn and Seijo (1944) and Lankford (1945) ; for the

Brucella group, by T'ung (1944); for B. ducreyi, by Mortara, Feiner and Levenkron (1944); for the Gram-negative intestinal bacilli, by Thomas and Levine (1945); for B. proteus, by Stewart (1945); for B. influenzæ, by Gordon and Zinnemann (1945); and for a variety of species, by Selbie, Simon and McIntosh (1945) and Meads, Ory, Wilcox and Finland (1945). Considerable variation, up to ten-fold or one hundred-fold, was commonly found in the sensitivity of different strains of a single species. Just as some strains of a normally " sensitive " species may be resistant to penicillin in concentrations of 0·1 to 0·3 units per ml., a few strains of a normally " resistant " species may prove sensitive to such concentrations; for example, two pathogenic strains of B. influenzæ (Forgacs and Hutchinson, 1945).

Comparison of the sensitivity measurements recorded by different authors is rendered uncertain because of differences in the size of the inoculum employed in the tests. It has been shown by Rammelkamp and Keefer (1943) and Hobby and Dawson (1944a) for Strept. pyogenes, by Rantz and Kirby (1944) and Kirby (1945a) for Staph. aureus, and by Shwartzman (1944) for B. coli, that greater concentrations of penicillin are necessary for the inhibition and killing of large numbers of organisms in a given volume of medium than for the inhibition and killing of small numbers in the same volume. Accordingly, in the present sensitivity examinations of different strains and species, the inoculum of organisms was kept, as far as practicable, at a constant size. The extent to which the results obtained are comparable is limited to the accuracy of the method for determining the inoculum size and, even more, where different conditions of culture had to be adopted.

METHOD

Except in the case of certain organisms which required special conditions for growth, all the tests were carried out in the following uniform manner. The inoculum was prepared from a twenty-four hours' culture; its size was controlled by taking a measured volume of an appropriate dilution of a bacterial suspension made up to a standard opacity. From 100,000 to 300,000 organisms were added to each of a series of tubes which contained, in 1 ml. of tryptic horse-flesh digest broth, the different concentrations of penicillin (as shown in Fig. 1). The penicillin was taken from a single batch of one commercial brand of the sodium salt (Pfizer); the contents of some ampoules of this batch had been assayed and found to contain the stated amount of penicillin. With each set of tests, a control test with the standard " Oxford " Staph. aureus was included. After twenty-four hours' incubation at 37° C., the tubes were examined for the presence of growth, as denoted by visible turbidity or deposit. In tests of B. pestis, the Brucella organisms, B. smegmatis, B. butyricus and B. phlei, a larger initial inoculum was used: from 1,000,000 to 3,000,000 organisms; the tubes were examined for growth after forty-eight hours as well as after twenty-four hours. Tests of the gonococcus, the meningococcus, B. influenzæ and B. pertussis were carried out in a different manner: a loopful of a suspension containing about 100,000,000 organisms per ml. was spread on the surface of each of a number of 10 per cent. blood agar plates which

incorporated the different concentrations of penicillin; after twenty-four and forty-eight hours' incubation the plates were examined for growth. In tests of the tubercle bacillus, a loopful of a culture suspension was spread on the surface of Lowenstein egg medium slopes; for each strain examined, two inoculated slopes were used as controls and other four were treated with penicillin in different concentrations, 0·15 ml. of solution containing 100,000, 32,000, 10,000 or 3200 units per ml. being introduced at the bottom of the sloped medium which was 1·5 ml. in volume. Assuming even diffusion of the penicillin throughout the medium, the final concentrations in the different tubes would be 10,000, 3200, 1000 and 320 units per ml. Fresh addition of penicillin was made every second day during incubation to allow for such inactivation as might occur. The penicillin concentration to which the tubercle bacilli were exposed must have varied considerably during the period of incubation; however, assays of the fluid at the bottom of the slopes suggested that, in the main, the concentration fluctuated about the initial level. The slopes were examined for growth at intervals during one month of incubation.

Sources of the Strains
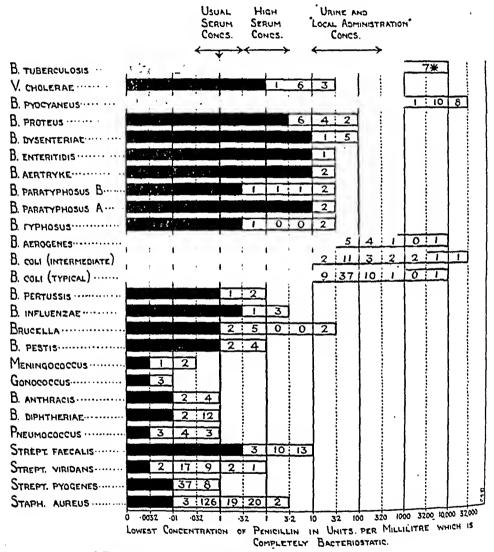
Old stock cultures were examined in the case of the gonococcus, the meningococcus, the Brucella group (3 abortus, 2 suis and 4 melitensis strains), B. anthracis, B. pestis, B. influenzæ, B. pertussis, B. typhosus, B. paratyphosus A and B, B. dysenteriæ (2 Shiga, 2 Flexner and 2 Sonne strains), V. choleræ, B. smegmatis, B. butyricus and B. phlei. The strains of the other species examined had been freshly isolated from human sources, where they had been present in a pathogenic or commensal rôle; except for some of the staphylococcal strains, they had *not* been exposed to penicillin treatment. The strains of Strept. fæcalis, B. coli, B. ærogenes, B. proteus, and B. pyocyaneus had been isolated from infected wounds, fæces, milk and urine. The strains of Strept. pyogenes, all of which produced soluble hæmolysin, had been recovered from the throats of patients with scarlet fever or tonsillitis. The strains of Strept. viridans had been isolated from the saliva of normal persons and the blood of patients with subacute bacterial endocarditis. All of the strains of Staph. aureus were coagulase positive; about *half* were from infections such as osteomyelitis, breast abscess, hand suppuration and septicæmia, about *quarter* from the anterior nares, skin and clothing of healthy persons and about *quarter* from infected wounds of patients who had received a short prophylactic course (a few days in duration) of systemic penicillin treatment.

Results

The results of the investigation are illustrated in Fig. 1. This shows the number of strains of each species which were just susceptible to each of the different concentrations of penicillin (*e.g.* the Fig. "2," for B. ærtryke, placed between the abscissæ for 10 and 32 units per ml., denotes that, in tests of *two* strains of B. ærtryke, growth took place in the presence of 10 units per ml., but not in the presence of 32 units

per ml.).   In the case of several species, there was a great difference in sensitivity between the least sensitive and the most sensitive strains. This difference was one hundred-fold in the case of Staph. aureus, Strept. viridans, Br. melitensis and B. ærogenes, and was one thousand-

SUSCEPTIBILITY OF DIFFERENT ORGANISMS TO THE ACTION OF PENICILLIN.

(SHOWING THE NUMBER OF STRAINS OF EACH SPECIES WHICH WERE JUST INHIBITED BY EACH DIFFERENT CONCENTRATION OF PENICILLIN.)

	USUAL SERUM CONCS.	HIGH SERUM CONCS.	URINE AND LOCAL ADMINISTRATION CONCS.
B. TUBERCULOSIS			7*
V. CHOLERAE		1 6 3	
B. PYOCYANEUS			1 10 8
B. PROTEUS		6 4 2	
B. DYSENTERIAE		1 5	
B. ENTERITIDIS		1	
B. AERTRYKE		2	
B. PARATYPHOSUS B		1 1 1 2	
B. PARATYPHOSUS A		2	
B. TYPHOSUS		1 0 0 2	
B. AEROGENES			5 4 1 0 1
B. COLI (INTERMEDIATE)			2 11 3 2 2 1 1
B. COLI (TYPICAL)			9 37 10 1 0 1
B. PERTUSSIS		1 2	
B. INFLUENZAE		1 3	
BRUCELLA		2 5 0 0 2	
B. PESTIS		2 4	
MENINGOCOCCUS	1 2		
GONOCOCCUS	3		
B. ANTHRACIS	2 4		
B. DIPHTHERIAE	2 12		
PNEUMOCOCCUS	3 4 3		
STREPT. FAECALIS		3 10 13	
STREPT. VIRIDANS	2 17 9 2 1		
STREPT. PYOGENES	37 8		
STAPH. AUREUS	3 126 19 20 2		

0   ·0032   ·01   ·032   1   ·32   1   3·2   10   32   100   320   1000   3200   10,000   32,000

LOWEST CONCENTRATION OF PENICILLIN IN UNITS PER MILLILITRE WHICH IS COMPLETELY BACTERIOSTATIC.

*EXACT LEVELS UNCERTAIN—SEE TEXT.

FIG. I.

fold in the case of B. coli.   Similar great variation in sensitivity might have been found in the case of some of the other species, if a larger number of strains of these species had been examined.

When the strains of Staph. aureus were grouped according to their source, it was found that the proportion of " resistant " strains was

not the same in each of the different groups. This differentiation was observed in a series of examinations by the " agar plate and gutter test " on a somewhat extended range of strains.* Of 95 strains isolated from closed infective lesions such as osteomyelitis, breast abscess and septicæmia, only one (1·1 per cent.) was " penicillin resistant "; of 66 strains isolated from the anterior nares, skin and clothing of healthy persons, three strains (4·5 per cent.) were " penicillin resistant "; and of 49 strains isolated from infected war wounds subsequent to systemic penicillin treatment, eighteen strains (37 per cent.) were " penicillin resistant." It is of interest to compare these results with the findings of Gallardo (1945); of 85 strains of Staph. aureus isolated from wounds prior to penicillin treatment, Gallardo found that 13 per cent. were " penicillin resistant," and that a further 9 per cent. acquired resistance during the subsequent penicillin treatment (see also Plough, 1945).

As will be seen from Fig. 1, penicillin in a concentration of 0·1 units per ml. was inhibitory for most strains of the species normally considered " penicillin sensitive," and was not inhibitory for any strains of the species normally considered " penicillin resistant." Some strains of Strept. fæcalis, B. pestis, the Brucella group, B. influenzæ, B. pertussis, B. typhosus and B. paratyphosus B were susceptible to penicillin in concentrations of 1 and 3·2 units per ml. As such concentrations are obtained in the serum during systemic administration of large doses, systemic infections with these partially resistant organisms may in some cases respond to penicillin treatment. Many strains of almost all the " penicillin resistant " species were found to be susceptible to penicillin in concentrations of from 10 to 320 units per ml. Penicillin concentrations of this order are readily attained in the urine and in the exudates of locally treated cavities and surfaces. It is possible, therefore, that urinary infections and accessible local infections, caused by the Gram-negative bacilli, may in many cases be amenable to penicillin treatment. It must be remembered, however, that the numbers of organisms present in infected exudates and urine may be much greater than the numbers of organisms initially present in the sensitivity test mixtures; when this is the case, higher concentrations of penicillin will be required than those indicated by the results of the sensitivity tests. For example, a strain of B. coli which was susceptible to 32 units per ml. when the inoculum was 300,000 organisms per ml., was not susceptible to less than 100 units per ml. when the inoculum was 30,000,000 organisms per ml.

The most resistant organisms encountered, which were able to grow freely in penicillin concentrations of 320 units per ml. or higher, included a few of the strains of B. coli and B. ærogenes, and all of the tested strains of B. pyocyaneus, B. tuberculosis and the saprophytic acid-fast bacilli. Even these very highly resistant organisms, however, were found to be inhibited by penicillin when the concentration was

* Carried out in collaboration with Dr S. W. Challinor of this department.

sufficiently increased. The strains of B. pyocyaneus, B. coli and B. ærogenes were inhibited by 1000, 3200, 10,000 or 32,000 units per ml.; the acid-fact saprophytes were susceptible to 1000 units per ml.; the strains of B. tuberculosis failed to grow in the culture tubes to which 3200 or 10,000 units per ml. were added every second day. Thus, under the conditions of these tests, *absolute resistance to the action of penicillin was not found in the case of any species or strain examined.*

THE ACTION OF PENICILLIN ON " RESISTANT " ORGANISMS

It was necessary to consider the possibility that the inhibition of growth of the more resistant organisms by strong solutions of penicillin was not due to the specific activity of the penicillin, but was due instead to some non-specific activity of the penicillin or of the impurities present in the preparation used. It is not thought that this was the case; evidence was obtained in several ways to suggest that inhibition was indeed due to the specific activity of penicillin. *Firstly*, the inhibitory action of the penicillin solutions on " resistant " organisms was annulled by the addition of penicillinase. *Secondly*, the action of penicillin on " resistant " organisms was similar to its action on " sensitive " organisms, as regards its relationship to the size of the inoculum and the nutrient character of the medium. *Thirdly*, similar characteristic morphological changes were produced in the " sensitive " and in the " resistant " organisms by effective concentrations of penicillin.

The Effect of Penicillinase.—Experiments to show that inhibition was annulled by penicillinase, were carried out with sodium penicillin (the Pfizer penicillin, and also Glaxo penicillin of 669 units per mg.). The penicillinase * used was the filtrate of a B. subtilis broth culture prepared in the presence of penicillin. In parallel with the usual sensitivity test for each strain, a test was carried out in which each of the different penicillin concentrations was made up in a mixture of 0·1 ml. of penicillinase solution and 0·9 ml. of broth. The mixtures were allowed to stand for one hour before inoculating and incubating. Tests were carried out in this manner with twelve strains of B. pyocyaneus, nine strains of intermediate B. coli, two strains of typical B. coli, two strains of B. ærogenes and one strain each of the smegma bacillus, the butter bacillus and the timothy-grass bacillus. In every case the presence of penicillinase was found to allow growth of the organism in penicillin concentrations which otherwise would have been inhibitory. Thus, in tests with the Glaxo penicillin, the smegma bacillus, the butter bacillus and the timothy-grass bacillus were found to be inhibited by a penicillin concentration of 1000 units per ml. in the absence of penicillinase, while not to be inhibited even by a concentration of 3200 units per ml. in the presence of penicillinase; (some

* Prepared by Miss M. L. Campbell-Renton and Dr S. W. Challinor of this department.

inhibition, presumably non-specific, was given by 10,000 units per ml. in the presence of penicillinase). Six strains of B. pyocyaneus were tested against the Pfizer penicillin and another six against the Glaxo penicillin ; in the absence of penicillinase, growth was inhibited by 10,000 or 32,000 units per ml., while in the presence of penicillinase no strain was inhibited by 32,000 units per ml. In tests with the Glaxo penicillin, the strains of B. coli and B. ærogenes were inhibited variously by concentrations of from 100 to 10,000 units per ml. in the absence of penicillinase ; in the presence of penicillinase, no inhibition was given by 10,000 units per ml.

The Bactericidal Action of Penicillin.—The mode of action of penicillin on " resistant " organisms was found to be similar to its mode of action on " sensitive " organisms. When sub-inoculations (by " plating out ") were made from the sensitivity test mixtures, first before and then after incubation, it was found that effective concentrations of penicillin killed the organisms initially present and did not merely inhibit growth ; this was demonstrated in the case both of " sensitive " and of " resistant " organisms. Furthermore, when inocula of different sizes were tested in this way (*e.g.* 10^8, 10^7, 10^6, 10^5, 10^4 and 10^3 organisms per ml.), it was found that greater concentrations of penicillin were required to inhibit and kill the larger than the smaller inocula : a doubling of penicillin concentration was often required for a hundred-fold increase in the size of the inoculum. This was demonstrated both for the " sensitive " organisms Staph. aureus, B. anthracis and B. diphtheriæ, and for the " resistant " organisms B. pyocyaneus, B. phlei and B. coli (*cf.* Shwartzman, 1944). The dependence of bactericidal action and rate of killing by penicillin upon the nutrient character of the medium has been established in the case of " sensitive " organisms by several investigators (Bigger, 1944 ; Hobby and Dawson, 1944*b* ; Lee, Foley and Epstein, 1944 ; Miller and Foster, 1944 ; and Todd, 1945). In the present investigation, the same relationship of the bactericidal action to the nutrient character of the medium was found in the case of a " resistant " organism, B. ærogenes. Changes in the viable count, during twenty-four hours' incubation in the absence of penicillin and in the presence of 1000 units per ml., were observed in cultures inoculated with 100,000 organisms per ml. When a highly nutrient medium was used (*e.g.* nutrient broth, peptone water, or a dextrose and ammonium salt solution), B. ærogenes multiplied *rapidly* in the absence of penicillin (an increase of one thousand to ten thousand-fold in the first eight hours) and was *rapidly* killed in the presence of penicillin (a reduction of one thousand to ten thousand-fold in eight hours). When a poorly nutrient medium was used (*e.g.* saline, tap water or Locke's solution), multiplication was very *slow* in the absence of penicillin (three to thirty-fold in the first eight hours) ; correspondingly, in the presence of penicillin, killing was also *slow* (ten to three hundred-fold in eight hours).

The Morphological Changes Produced by Penicillin.—Gardner (1940 and 1945) has described certain morphological changes which are produced by penicillin in both "sensitive" and "resistant" organisms. In the present investigation, a study was made of the morphological changes undergone by B. pyocyaneus, B. proteus, B. coli, B. aerogenes, B. paratyphosus B, V. cholerae, B. pestis, B. anthracis B. diphtheriae, Staph. aureus and Strept. pyogenes. These organisms were observed directly (unstained) while growing on blocks of nutrient agar which incorporated different concentrations of penicillin and

FIG. 2.—The effect of penicillin on growth of B. coli.

which were mounted between a slide and coverslip under an incubated microscope. Essentially the same sequence of changes was found to occur in the "resistant" as in the "sensitive" organisms, although, as might be expected, the exact features presented were to some extent dependent on the initial morphological type of the organisms. (See Fig. 2 for a diagrammatic representation of the changes shown by Gram-negative bacilli in the unstained state.)

(1) *At penicillin concentrations in the neighbourhood of,* e.g. *from one-third to thirty times, the lowest inhibitory concentration for the strain.* There was an initial period of growth which usually lasted for four, five or six hours, but which might be prolonged up to ten hours or even longer with the lower penicillin concentrations, and shortened

to two or three hours with the higher concentrations. During this period, some multiplication took place, together with considerable enlargement of the individual cells ; a single bacterium of the inoculum often gave rise to two, four or eight abnormal giant cells which were destined ultimately to die as a result of the action of the penicillin. Death of the organisms, which terminated the period of growth, was usually marked by visible lysis. In many species, lysis was initiated by the protrusion of " bubbles " of protoplasm. The organism would then become paler in appearance and either disappear entirely or remain visible as a delicately outlined, empty or slightly granular " ghost." Lysis sometimes occurred rapidly, in the course of a few minutes, and sometimes gradually, during the course of an hour or so.

In the case of the Gram-negative bacilli and V. choleræ, enlargement took the form of elongation into filaments of 10, 20, 30 or even 100 microns in length. A large proportion of the filaments developed, at one or more points in their length, spindle-shaped or spherical swellings, from 2 to 5 microns in breadth ; most commonly, a single swelling was found in the middle of a filament, at the site of what appeared to be a transverse septum incapable of developing to the stage of complete fission. In preparations stained by the method of Robinow (1944) for demonstrating cytoplasmic boundaries, the transverse equator of each swelling was seen to be occupied by a band or rounded body, which was intensely stained like the cytoplasmic boundaries ; deeply stained transverse bands were also seen at intervals along the filaments, representing perhaps imperfectly formed boundaries between the component bacterial units. When stained by Robinow's method for demonstrating chromatinic (" nuclear ") bodies, each filament was found to contain these bodies, usually as single or paired transverse rods, distributed in a fairly regular manner along its length ; in the swellings, the chromatinic bodies were clustered irregularly and were usually absent from a large central area which apparently corresponded to the equatorial cytoplasmic mass. Up to the stage of filament formation and swelling, the abnormal cells were apparently alive, for growth and " nuclear " division had been proceeding and normal motility was exhibited in the case of the motile strains (e.g. of B. proteus and V. choleræ). Lysis, and thus death, of the filamentous cell was in most cases initiated by the gradual or sudden protrusion, usually from the region of a swelling, of one, two or sometimes more " bubbles " of protoplasm, which varied in diameter from 1 to over 10 microns and which contained numerous chromatinic bodies ; following this, the filament became pale, or even disappeared entirely. Some filamentous cells underwent lysis without any visible protoplasmic protrusion, and some without even having developed a swelling.

In the case of B. anthracis (see Mackie, 1946 ; figure), single bacilli developed into short chains of from two to eight swollen, oval or spherical cells ; these were from 2 to 4 microns in transverse

diameter. Lysis was sometimes initiated by the protrusion of visible " bubbles " of protoplasm. The swollen bacilli shrivelled up, became pale and either disappeared or remained visible as empty " ghosts." In the case of B. diphtheriæ gravis, single bacilli developed into short filaments which consisted of from two to eight cells, marked off from each other by transverse septa, but seldom accomplishing complete fission and separating in the normal manner ; some cells became swollen, up to 2 or 3 microns in breadth. A proportion of the cells underwent lysis, becoming pale and empty looking ; there was no visible protoplasmic protrusion. In the case of Staph. aureus and Strept. pyogenes, swollen, spherical and oval forms were developed, of up to 2 or 3 microns in diameter ; multiplication was often marked by incomplete fission, resulting in the formation of clusters of incompletely separated staphylococci and spindle-shaped chains of closely fused, giant streptococci. A proportion of the cells underwent lysis ; these merely became pale and did not show any visible protoplasmic protrusions. The swollen cells which remained unlysed appeared to be dead ; when placed on fresh nutrient agar, they did not again begin to grow.

(2) *At penicillin concentrations much higher*, e.g. *over thirty times higher, than the lowest inhibitory concentration.* There was no initial period of growth. The cells did not enlarge by elongation or swelling, and they did not multiply except for the occasional completion of a single division. Lysis usually took place within one or two hours. The Gram-negative bacilli became pale or disappeared entirely, sometimes after the protrusion of small " bubbles " of protoplasm and sometimes without this occurring. B. anthracis became very pale, or disappeared entirely, without visible change in shape or protoplasmic protrusion. B. diphtheriæ, Staph. aureus and Strept. pyogenes showed little change.

This sequence of morphological changes exhibited both by " sensitive " and by " resistant " bacteria, appears to be related essentially to the bactericidal action of penicillin. None of the changes were due to the action of impurities present in the commercial penicillin preparations, for exactly the same changes were produced by pure crystalline sodium penicillin (1600 units per mg.) in tests with B. anthracis, B. proteus, B. aerogenes and B. coli.

CONCLUSIONS

It appears that all bacteria (within the limits of this investigation) are susceptible in some degree to the specific activity of penicillin. If this is so, the metabolic mechanism or cellular component upon which penicillin exerts its effect, must be possessed in common by all bacterial species. Variations in *degree* of sensitivity may be due to a variety of factors ; in some cases, a high degree of resistance may be due to penicillinase production (Bondi and Dietz, 1944 and Kirby,

1945*b*). Little is known about the mechanism of the bactericidal action of penicillin, beyond that only actively metabolising and growing cells are susceptible. The morphological changes described above as produced by the lower penicillin concentrations, in particular the failure of proper cell division and the ready occurrence of swelling and protoplasmic protrusion, suggest that penicillin in these concentrations interferes specifically with the formation of the outer supporting cell wall, while otherwise allowing growth to proceed until the organism finally bursts its defective envelope and so undergoes lysis. In the higher concentrations, penicillin must act somewhat differently.

SUMMARY

1. Quantitative measurements of sensitivity to penicillin have been carried out on a number of strains of each of a variety of bacterial species.

2. Many strains of those organisms which are usually considered " penicillin resistant " were found to be susceptible to penicillin in concentrations obtainable in infected body fluids.

3. Under the conditions of the tests, absolute resistance to the action of penicillin was not found in the case of any of the strains or species examined.

4. Reasons are given for believing that the nature of the action of penicillin on " resistant " organisms is essentially the same as the nature of its action on " sensitive " organisms. The action of penicillin on " resistant " organisms is annulled by penicillinase. As with " sensitive " organisms, the action of penicillin on " resistant " organisms is bactericidal and not merely bacteriostatic ; the lowest bactericidal concentration varies with the initial number of organisms present in a given volume of medium ; the rate of killing varies with the nutrient value of the medium. Similar characteristic morphological changes are produced in " sensitive " and in " resistant " organisms by effective concentrations of penicillin.

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WARTIME ADVANCES IN MEDICINE WHICH MIGHT BE TRANSLATED INTO CIVIL PRACTICE *

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IN a world war many long-standing medical problems assume such vital importance to the fighting services that a solution must be found at all costs. During the recent war, service medicine has led to major progress in our knowledge of several important fields. Minor advances have also been recorded and there is much that can be translated to civil medicine.

Preventive medicine is of first importance in war and here the greatest strides have been made during the war years.

CONTROL OF INSECTS AND OTHER PESTS

(1) *Insecticides.*—The two insecticides which were most widely employed in pre-war days were pyrethrum and derris, but on the entry of Japan into the war the supply of these had been largely reduced. In 1942 dichlordiphenyl-trichlorethane (D.D.T.) came to the notice of the British and United States Governments, who at that time were seeking a substitute for pyrethrum and derris, the two natural insecticides hitherto used to combat the insect vectors of malaria and typhus. This multi-purpose insecticide has proved to be the outstanding recent achievement in the field of preventive medicine.

Extensive trials with D.D.T. have demonstrated that it is an ideal insecticide because it is highly lethal to insects as a contact and stomach poison and of low toxicity to man. D.D.T. is very effective against mosquitoes, sandflies, house flies, bed-bugs, cockroaches, lice and fleas. Because of its great stability it has a remarkable residual effect unequalled by other insecticides. It has therefore been used with great effect as a residual spray on walls indoors and on vegetation and other material out-of-doors. An extensive field trial indicates that surfaces so treated remain lethal to insects coming in contact with them up to a month or more after the application of the D.D.T. A 5 per cent. concentration is suitable for most insecticidal purposes.

By applying this solution to the inside of houses as a residual spray mosquitoes, bugs and other insects coming in contact with these surfaces for long periods afterwards will be destroyed; similarly by spraying surfaces around cookhouses or other places where flies tend to collect these pests can be largely eliminated. In Burma it has

* A Honyman Gillespie Lecture delivered in the Royal Infirmary on 13th June 1946.

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been shown that by barrier spraying with a 5 per cent. solution of D.D.T. on the surrounding ground outside the huts to a depth of fifty yards, in addition to inside spraying, a very great reduction in the mosquito population can be effected. Considerable difficulties have been met with in spraying D.D.T. from aircraft, especially when weather conditions are unsuitable for flying. An interesting story is told of the behaviour of the local population in one area where air spraying was being done; they all rushed into the open immediately the plane was heard, their object was not to see the plane but to get some of the D.D.T. on their heads for they had discovered what an excellent lousicide it was.

It can be easily understood what a boon D.D.T. has proved in combating insect-borne diseases such as malaria, sandfly fever, leishmaniasis, dengue, trypanosomiasis, dysentery, typhoid, epidemic typhus and plague. In addition, it is a great relief to be free from the vexation caused by the bed-bug and other biting creatures.

In 1942 Imperial Chemical Industries discovered another insecticide, benzene hexachloride (666), which has similar insecticidal properties to D.D.T.; so far this has not been given any large scale trial by the services.

(2) *Repellents.*—Early in the late war the discovery of the insect-repellent properties of dimethylphthalate (D.M.P.) was of outstanding importance. It rapidly superseded citronella oil and despite the vast amount of research in the field, D.M.P. is still pre-eminent. Applied to the skin it gives protection against biting insects for two to three hours. Even in this country it has a place in saving us from the biting midge and the harvest bug. It has been proved that a high degree of protection against insect bites can be achieved by wearing over the exposed parts of the body D.M.P.-impregnated veils, gloves, socks, etc., made of strong ⅜-in. fish net material. The netting holds the repellent so that it requires reimpregnation only once a week. To be effective, however, this must be worn next to the skin and have no other garment over it.

(3) *Miticides.*—D.M.P. has a marked lethal effect on the mite and is therefore of value for protection against the mite typhus (scrub typhus). The plan is to smear D.M.P. on the clothing at regular intervals. Dibutylphthalate (D.B.T.), however, has been shown to be more persistent; it withstands exposure to damp conditions for longer than D.M.P. Applied to garments, it is effective for from seven to fourteen days under tropical conditions. For this reason D.B.P. has been adopted by the British service as the anti-mite fluid for application to garments as a protection in scrub typhus countries. Benzyl benzoate is also showing considerable promise against mites, both in the laboratory and the field.

A " Summary of Information on Insecticides and Repellents " is contained in a publication from the office of the scientific advisers (chemistry) Ministry of Production.

SCABIES

Prior to the late war scabies was treated almost entirely by sulphur which entailed baths before applying the ointment. Now in the service the disease is largely treated with benzyl benzoate lotion or emulsion. This can be applied to the untreated skin with a brush, or better still, the patient can dip his hands in the solution and apply it to every inch of the skin below the neck. Two applications should be made with an interval of fifteen minutes between on each of two successive days ; no further application should be made after this for at least ten days. The clothes are put on directly over the emulsion thus allowing enough of the drug to come in contact with any of the parasites which may be on the underclothing. Separate disinfestation of the clothes is not, therefore, required except in unusually severe cases.

HEAD LICE

Buxton's work has led to the thiocyanates being very largely employed for destruction of head lice in the women's services. The results have been so satisfactory that medicated hair oils containing thiocyanates are now available for purchase by the general public. Trials with D.D.T. emulsions against *Pediculus capitis* are giving very good results but toxicity tests are not yet complete.
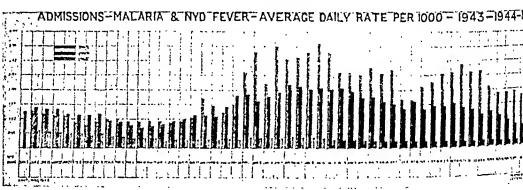
MALARIA

At the beginning of this war malaria was our greatest problem in most of the overseas theatres of war. In Burma it was the cause of nearly half of all the total sickness and in the season of highest incidence it was responsible for 80 per cent. of all admissions to hospital. Fortunately, great advances have been made in the methods of personal protection against this disease—methods that are applicable even when troops are situated in areas where permanent anti-mosquito measures cannot be carried out ; malaria is thus open to attack at many points. Mosquitoes—adults as well as larvæ—can be destroyed by D.D.T., biting can be prevented by the wearing of protective clothing and the use of repellents (D.M.P.), and finally, even when men are bitten by infected mosquitoes, the disease can be kept from causing clinical symptoms by the use of suppressive mepacrine (atebrin). When Java was lost and we had to find a substitute for quinine against malaria, mepacrine was the drug selected for this purpose. At that time (1942) our knowledge of the best way of using mepacrine against malaria was very incomplete, and an enormous amount of field, laboratory, and clinical research had to be undertaken before we learned all that we now know about suppressive mepacrine.

To enable these researches to be carried out in this country volunteers came forward ; these volunteers included members of the Friends Ambulance Unit, students at Oxford University where the Army Malaria Research Unit was located, and serving soldiers for

the work at the Royal Army Medical College. They took varying doses of mepacrine over prolonged periods in order that we might observe the effect of the drug on their health, study its behaviour in the body, and learn more about its action on malaria parasites. Innumerable observations on blood levels were made; tests were carried out on the functions of the liver and other organs of those who had been on the drug for long periods in order to determine whether any ill-effects were being produced; and many volunteers submitted to infection with subtertian (*P. falciparus*) malaria so that accurate information could be obtained about the best method of using mepacrine. It was found that the best all-round method of suppressing malaria was the regular, daily administration of o·1 gm. of mepacrine given under strict supervision and continued for as long as the person was under the risk of infection and for one month

TABLE I

ADMISSIONS—MALARIA & NYD FEVER—AVERAGE DAILY RATE PER 1000—1943—1944

after he left the malarious area. When this procedure is properly carried out, the results are beyond question. It may be said, for all practical purposes, that clinical attacks of malaria cease to occur. Moreover, if the continuation course is kept up for one month afterwards, those who have been infected with subtertian malaria will be cured—their dangerous infection will not relapse. On the other hand, attacks of benign tertian (*P. vivax*) malaria will still occur after the drug is stopped, and these attacks have to be treated on the usual lines. The employment of suppressive mepacrine in highly malarious regions has been the greatest single factor in maintaining our forces in these areas in a condition fit to fight and defeat the enemy (Table I).

Besides more effectively suppressing malaria, mepacrine has the additional advantage over quinine that it does not precipitate blackwater fever; in fact, since quinine has been given up, this much dreaded and dangerous complication has almost entirely disappeared from areas which were formerly notorious for its presence. Furthermore, those who take suppressive mepacrine regularly do not develop the severe cerebral and other complications which were so often a cause of death in pre-mepacrine days.

Much has been done to discover the best method of bringing about a radical cure of B.T. malaria (*P. vivax*). Massive doses of mepacrine have not given the results that some expected. Observations on the relapse rates of a carefully followed-up series of cases of relapsing B.T. malaria treated in this country indicate that combined treatment with quinine and pamaquin (plasmoquin), 30 grains of quinine and 0·03 gm. of pamaquin given daily for ten days, secures by a long way the greatest number of radical cures (Table II). Patients on this

TABLE II

Treatment of Relapsing B.T. Malaria contracted in the Central Mediterranean Area—Extract from D.B.R. Interim Report on Malaria Relapses after Treatment with Quinine and Synthetic Quinine Substitutes.

Records examined after a follow-up five months later showed :—

Relapses after Treatment.	Course M.		Course QP.	
	Number of Cases.	Per Cent. of All Cases.	Number of Cases.	Per Cent. of All Cases.
None	429	66·0	524	89·7
1	184	28·3	56	9·6
2	33	5·1	4	0·7
3	4	0·6	0	...
Total relapsed cases	221	34·0	60	10·3

(1) *Mepacrine* (M) *Course.*—0·8 gm. daily for two days then 0·3 gm. daily for ten days. Total dose 4·6 gms.

(2) *Quinine pamaquin* (QP) *Course.*—Quinine grains 30 pamaquine 0·03 gm. daily for ten days.

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treatment must, however, be under medical observation during the whole period, so that the pamaquin can be discontinued if signs of toxicity appear. Hæmoglobinuria has occurred in a few patients taking pamaquin, but this has not been a source of trouble in British patients. In Indians, however, the occurrence has not been infrequent and for this reason if administered the daily dose should be reduced to 0·02 gm.

A new compound, SN 13276, closely allied to pamaquin, has been produced in the United States; this is said to be a less toxic drug than pamaquin but to have all the anti-malarial properties of the old drug. If this proves to be correct and we can safely give it in larger doses, then it should prove a valuable preparation for the eradication of relapsing B.T. malaria.

While the patient is still residing in a malarious area, treatment of a clinical attack of uncomplicated malaria is nowadays usually carried out with mepacrine alone. During the first two days of treatment, relatively large doses are given to secure a rapid concentration of drug in the blood and tissues, and this is maintained by a smaller

daily dose during the remainder of the treatment. A total of 0·6 to 0·8 gm. of mepacrine is a suitable daily dose for an adult on the first two days, and a daily maintenance dose of 0·3 gm. is usually given for a further five days. Suppressive mepacrine treatment should then be commenced as soon as this treatment has been completed.

If after leaving a malarious area a patient develops frequent relapses, it is advisable to give him ten or fourteen days' quinine and pamaquin treatment to obtain a radical cure.

Major J. Innes, who until recently was in charge of No. 2 Malaria Research Team, has carried out some valuable research in malaria, first in the Central Mediterranean Force and later in this country. He has shown that any course of treatment for B.T. malaria containing pamaquin will give a lower relapse rate than treatment without pamaquin. His results indicate that intermittent quinine and pamaquin treatment of relapsing B.T. malaria given over a period of thirty-one days is likely to give the best results of all. On this treatment they received initially seven days of quinine (gr. 10) and pamaquin (0·01 gm.) given t.i.d. and then after a rest from drugs for seven days two further five-day courses of dosage with another interval of seven days between these courses. The total quinine given was 510 grains and pamaquin 0·51 gm., and so far no relapses have been reported. This course is less liable to cause toxic manifestation than the continuous dosage.

Intramuscular mepacrine given in doses of 0·2 to 0·4 gm. is extremely valuable for producing a very rapid concentration of mepacrine in the blood where this is required.

A NEW ANTI-MALARIAL DRUG

A new synthetic anti-malarial drug marketed by the British firm, Imperial Chemical Industries, may be expected to play an important part in the prevention and treatment of malaria.

Mode of Action.—Paludrine acts on the asexual parasites of the human cycle, apparently by inhibiting nuclear division. It has no detectable effect on the morphology of gametocytes in human blood, but if mosquitoes are fed on a human gametocyte-carrier while he is taking paludrine, the mosquitoes do not become infected. Oocyst formation fails in the mosquito, possibly because of some action of the paludrine in its stomach.

Perhaps even more important is the action of paludrine during the pre-patent phase of human malaria—the incubation period of ten days or so between the injection of sporozoites and the appearance of clinical symptoms and ring forms in the peripheral blood. At Cairns in Australia, Hamilton Fairley has shown that if 100 mgrms. (0·1 gm.) is given twice a week during this period, sporozoite-infected volunteers, bitten repeatedly by infected mosquitoes, fail to develop parasites in their blood. This observation rests on the stringent test

of sub-inoculation of 200 c.c. of blood into a second group of susceptible volunteers.

In subtertian malaria (*P. falciparum*), attacks of the disease do not follow when paludrine is stopped, the drug acting apparently as a true causal prophylactic. A single dose of 50 mgrms. during the pre-patent phase has produced the same effect. In benign tertian (*P. vivax*) malaria, on the other hand, 100 mgrms. of paludrine daily acted only as a suppressive because overt attacks followed cessation of treatment, although after a longer interval than with mepacrine given in the same way.

Therapeutic Use.—For treatment of clinical attacks the optimum dosage is not yet known. As much as 1 gm. daily has been given, but 250 mgrms. twice daily for seven to fourteen days will probably be sufficient. This should cure patients with subtertian (*P. falciparum*) malaria ; but treatment of benign tertian (*P. vivax*) relapses with paludrine has not given such good results as the ten- to fourteen-day quinine-pamaquin course.

Side Effects.—The drug is pleasant to take and it does not stain the skin. Undesirable effects are slight except with very large doses. Minor effects are vomiting and epigastric discomfort. With large doses evidence of renal irritation may appear : red blood cells and hyaline and granular casts in the urine.

DYSENTERY
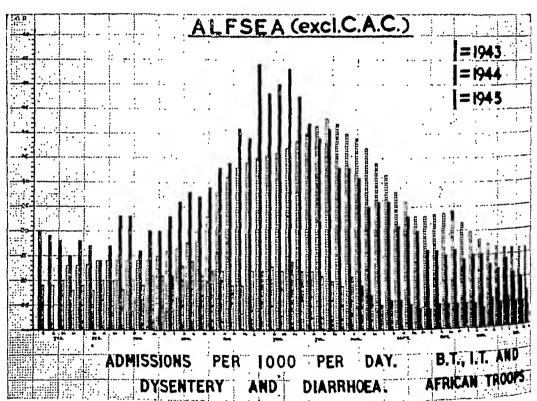
(1) *Bacillary Dysentery.*—Under primitive conditions of hygiene, bacillary dysentery is very likely to become prevalent. Such a state of affairs is often inevitable for an army living under active-service conditions, and this form of dysentery has therefore been responsible for much loss of manpower in the services, especially in tropical or sub-tropical areas.

In the early days of the recent war, the dysentery rate was high and many patients suffered from extremely severe infection which ended fatally in some instances. The Middle East Forces turned to the sulphonamide drugs for the treatment of this disease with very promising results. The preparation which the British Army has largely used is sulphaguanidine ; the United States forces, however, prefer sulphadiazine and claim that the results with this drug are superior to those with sulphaguanidine. There is evidence to support the view that almost any of the sulphonamide preparations are of value in the treatment of bacillary dysentery ; but if the patient is dehydrated, especially if he is in a tropical country where much fluid is lost by sweating, then as a safeguard against kidney damage sulphaguanidine is the preparation of choice. Owing to the absence of urinary complications during the administration of sulphamezathine this preparation should be a valuable one for use in bacillary dysentery. Shortage of supply, however, did not permit of its wide use in this

disease during the war years. Phthalyl sulphathiazole, owing to its powerful action against bowel organisms, should also be a useful preparation.

To ensure the best results, it is important to begin treatment at the earliest possible moment. The Army, therefore, felt justified in recommending that any acute diarrhœa should be treated with sulphaguanidine without waiting for laboratory confirmation. Since this policy has been adopted, really severe attacks of bacillary dysentery have seldom been encountered, and the results of treatment with sulphaguanidine have been very satisfactory. In forward areas

TABLE III

sulphaguanidine was issued to small detached parties of men so that they could carry out treatment themselves. The usual dose is 5 gms. every three hours for the first twenty-four hours; thereafter the dose is reduced and the interval lengthened according to the patient's response. As a rule, a total dosage of about 100 gms. is adequate for the treatment of a patient with bacillary dysentery (Table III). In isolated communities this method of treating bacillary dysentery is of great value because the patient can be treated locally and long and difficult journeys thus avoided. Anti-dysenteric serum is now very rarely required in the treatment of patients suffering from bacillary dysentery. Reports from United States Army sources suggest the value of giving sulphonamide as a prophylactic at the commencement

of an outbreak of bacillary dysentery in a unit to prevent the spread of the disease.

Bacteriophage Treatment.—It was shown by Boyd and Portnoy [1] in the Middle East Force that this form of treatment was of no value. Conversations with captured German medical officers revealed that they had reached the same conclusions.
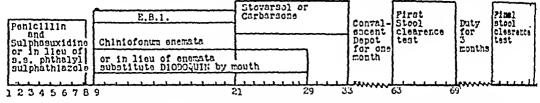
The value of D.D.T. in the control of flies and the spread of dysentery has been mentioned under insecticides. The absence of flies where D.D.T. residual spray has been properly applied to the right places is very striking. It should be remembered, however, that in practice D.D.T. is only effective against the adult fly; once the egg has been laid it will not prevent the further development up to pupation.

(2) *Amœbic Dysentery.*—Large numbers of our troops have had to operate in countries where amœbic dysentery is prevalent. As a result much experience has been gained in the treatment of this disease. Many patients evacuated from overseas have arrived in this country with a very intractable form of amœbic dysentery which had resisted all the usual methods of treatment. It seemed a fair assumption that invasion of the damaged intestinal walls by secondary pyogenic organisms might play an important part in these intractable cases that are unresponsive to ordinary combined courses of treatment with emetine, emetine bismuth iodide (E.B.I.) and chiniofon. Therefore an attempt was made to deal with these organisms by a preliminary course of penicillin and sulphonamide.

W. H. Hargreaves [2] has shown that such a preliminary course may bring about conditions that permit a favourable response to emetine therapy in patients who have previously resisted all ordinary forms of treatment and have progressively deteriorated into a poor state both physically and mentally. The course to eliminate secondary pyogenic organisms which has been found to give the best results is as follows: give 30,000 units intramuscularly every three hours until 2,000,000 units have been administered. At the same time give sulphasuxidine 20 gms. or phthalyl sulphathiazole 10 gms. daily for the same period. If necessary, sulphadiazine, sulphathiazole, or sulphaguanidine may be used in appropriate dosage. This preliminary course does not eradicate the specific (amœbic) infection but it certainly paves the way for cure by one of the ordinary anti-amœbic courses. Accordingly, the usual course of oral E.B.I., chiniofon retention enemas, or diodoquin, and the follow-up course of stovarsol or carbarsone is begun as soon as the preliminary course of penicillin and sulphonamide has been completed. It is essential to ensure that E.B.I. is given in a readily absorbable form, preferably in a gelatine coated capsule. This great advance in the treatment of resistant cases of amœbic dysentery has changed the whole outlook for patients whose infection had previously resisted all attempts at cure (Table IV).

TABLE IV

Treatment of intractable cases of amoebic dysentery that resist ordinary treatment.

Penicillin and Sulphasuxidine or in lieu of s.s. phthalyl sulphathiazole	E.B.1.		Stovarsol or Carbarsone		Conval-escent Depot for one month	First Stool clearance test	Duty for 3 months	Final stool clearance test
	Chiniofonum enemata							
	or in lieu of enemata substitute DIODOQUIN by mouth							

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  1 2 3 4 5 6 7 8 9              21      29  33        63        69
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Day 1-8.   Penicillin 30,000 units intramuscularly every 3 hours for 8 days combined with sulphasuxidine 20 grams daily for the same period ; or phthalyl sulphathiazole 10 grams instead of sulphasuxidine.

Day 9-21.   Emetine bismuth iodide grs. iii given in a readily absorbable form by mouth on an empty stomach each night, together with Chiniofonum (Yatren) retention enema 2½ per cent. or 4 per cent. each morning, 250 c.c. to be retained for 8 hours.

Day 9-29.   In lieu of chiniofonum retention enemy a 20 days' course of diodoquin may be given by mouth consisting of 3 pills (each contain 0·2 gram.) three times a day for a total of 20 days, this ending on the 29th day of treatment.

Day 21-33.   Stovarsol or carbarsone tablets (0·25 gram.) one twice a day for 12 days.

The patient may be allowed out of bed after the 21st day of treatment and can complete his course at a convalescent home or depot.

Tests of cure are not commenced until one month after completing the treatment when specimens should be examined daily for 6 consecutive days ; three months later a similar clearance test should be performed.

TYPHUS

(1) *Epidemic Typhus.*—Although our troops have fought in coun-tries where this disease was prevalent, the numbers who have contracted typhus have been very small.   We owe this to vaccination and the efficient use of anti-louse measures.   Owing to its persistent qualities D.D.T. is an ideal lousicide, garments may be impregnated or it may be dusted inside the garment of the wearer, if necessary without undressing.   Although it has no action on the egg its residual effects enables D.D.T. to destroy the larva when it emerges from the egg. Mechanised dusting enables large numbers of subjects to be treated quickly ; a 10 per cent. D.D.T. dusting powder is effective against lice.

(2) *Scrub Typhus.*—In Burma, where the infected mite vector is widespread, scrub typhus has been one of our great problems.   But the miticide dibutyl phthalate has led to great improvements.   There is also some evidence from animal experiments and the favourable outcome of laboratory infections in vaccinated human workers that the new cotton-rat vaccine may afford some protection against scrub typhus.   The large scale field trial of this new vaccine laid on in Burma is unfortunately unlikely now to provide any useful information owing to the unexpectedly rapid collapse of Japan and the withdrawal of troops as far as possible from the dangerous jungle areas.   Further-more, now that troops are static and so able to receive early treatment with adequate rest and nourishment from the earliest stages of the disease, the mortality in even the unprotected has fallen from over 10 per cent. to under 3 per cent.   The main cause of death is circulatory failure, and this danger is much increased unless the patient is kept at rest, especially after the fifth day of the disease.

TYPHOID FEVER

In this war sporadic cases have been very rare but there have been a few sharp outbreaks—among them, one of 80 cases in the 21st Army Group. In these outbreaks it was noted that the percentage of isolation by blood culture was very high ; this suggests that in favourable circumstances a series of negative cultures may be accepted as reliable evidence of non-infection. In accordance with previous experience, the mortality rate remains high in spite of inoculation. In the outbreak in 21st Army Group, 9 of the 80 cases died. This confirms the opinion that inoculation does not lessen the severity of the established disease. In this outbreak there was strong evidence to suggest that infection was acquired from milk so heavily infected that the dose of bacteria ingested was large enough to swamp the resistance afforded by inoculation.

Bacteriophage typing has proved its value for studies of typhoid epidemiology ; it was particularly useful in investigating cases among Italian and German prisoners captured by the Middle East Force.

SULPHONAMIDES

Nothing need be said on the use of these drugs in general, but it might be well again to emphasise the importance when using the drug in tropical climates, of guarding against the danger of kidney damage where the urine is scanty from excessive sweating and diseases in which diarrhœa is a marked feature ; sulphamezathine owing to its marked solubility in the urine is a valuable drug under these conditions.

The value of the sulphonamides in controlling cerebro-spinal fever may be mentioned. It has been shown that, if there is an increased incidence of this disease in a community, and the carrier rate is high, the administration of even small doses of sulphadiazine or sulphathiazole—3 gms. a day for three days—will reduce the carrier state to practically nil and stop the occurrence of further cases. On the other hand, attempts at chemoprophylaxis of respiratory diseases by the use of small daily doses of one or other of the sulphonamides have given disappointing results.

At one period the Army experienced considerable trouble from skin sensitisation that arose from the use of the sulphonamides as local applications. The incidence of this sensitisation was apparently greater in the Army than in civil life ; but it seems very likely that the discrepancy could be accounted for by better opportunities for observation and centralisation of reports, and that it did not prove any special effect of light and exposure.

Reports on the value of sulphathiazole for the control of pyogenic skin infection in smallpox are conflicting ; it is likely that penicillin will be more effective for this purpose.

PENICILLIN

Penicillin has been tried in the Army over a wide range of different conditions; the results have been much the same as in civil life. It was of uncertain benefit in a few cases of Weil's disease, but it is suggested that its earlier use in bigger dosage might show a more favourable picture. In severe cases of diphtheria, trials have been made with penicillin as an addition to the ordinary antitoxin therapy; evidence of its value is as yet inconclusive. There are indications, however, that penicillin given in the acute stage of the disease will reduce the convalescent carrier rate very considerably, although penicillin employed orally in diphtheria carriers does not appear to have any permanent beneficial effect in this respect, once the condition is established.

There is, however, good evidence that locally applied penicillin is of great value in the treatment of infective gingivitis. Application can be secured by oral lozenges or by a slow oral drip. Rat-bite fever (both forms) has been successfully treated by penicillin.

Homologous serum jaundice is just as likely to follow the administration of intramuscular penicillin as any other procedure involving the use of a syringe and needle. For example, patients under penicillin treatment for syphilis have been found to develop jaundice after the normal incubation period for homologous serum jaundice. This strongly supports the view, now generally accepted, that the jaundice which occurred in syphilitic patients under arsenical treatment was not caused by the arsenic but by transmission of the icterogenic agent from a former patient by the agency of an imperfectly sterilised syringe and needle.

Penicillin for Syphilis.—Penicillin therapy for syphilis is now well known in civil practice, but it may be worth recording the results of the Army follow-up of syphilis cases treated with 2·4 million units given over a period of seven and a half days. This course will cure practically all primary serum-negative cases—that is, cases with a primary lesion but without a positive Wassermann or Kahn reaction. The results in primary serum-positive cases are less satisfactory, and in secondary syphilis they are still less satisfactory. Figures from U.S.A. following this treatment indicate that the relapse rate after a year will be around 15 per cent. Modification in treatment by the addition of a follow-up course with arsenic and bismuth is therefore necessary.

LABORATORY DIAGNOSIS

(1) *Smallpox.*—A laboratory method for the diagnosis of smallpox, elaborated by Major C. E. van Rooyen, has proved useful in the differential diagnosis of smallpox and chickenpox in M.E.F. Smears are made from the contents of an early vesicle (it is essential that this should not have gone on to the stage of secondary infection)

and are stained by Paschen's method. In smallpox large numbers of elementary bodies are seen ; in chickenpox only a few granules at most. An experienced observer has no difficulty in differentiating between the conditions, but those without actual experience of the method are advised to examine the full details and advice given in the original article by C. E. van Rooyen and R. S. Illingworth.[3]

(2) *Typhus.*—An agglutination test has been evolved for the differentiation of louse-borne and flea-borne typhus fever.

Experimental work on the production of a vaccine to protect against typhus fever has resulted in the discovery of methods by which relatively pure suspensions of rickettsiæ can be prepared.

Major C. E. van Rooyen has shown that these suspensions can be used as antigens in an agglutination test, and has found that by this means it is possible to differentiate between louse-borne and flea-borne typhus fever. In louse-borne typhus fever the serum of a case about the fourteenth day agglutinates a suspension of " human " rickettsiæ (louse-borne) to about three times the titre to which it agglutinates a suspension of " murine " rickettsiæ (flea-borne).

Conversely in flea-borne typhus the serum agglutinates murine rickettsiæ on occasion as much as ten times the titre at which it clumps human rickettsiæ. C. E. van Rooyen, J. H. Bowie and K. S. Kirkorian emphasise that the granules which form are very delicate and some experience is necessary to read the results accurately.[4]

(3) *Tick-borne Relapsing Fever.*—Thick smear methods are essential for the diagnosis from blood smears. Spirochætes are usually so scanty that they are missed in thin smears.

(4) *Weil's Disease.*—Despite repeated warnings, the inexperienced continue to examine wet smears of blood by dark-ground illumination and to mistake " streamers " for leptospiræ. The nature of these " streamers " is obscure. They were originally thought to be organisms, but Wenyon later described " blood filaments " bearing a striking resemblance to leptospiræ in normal blood. They are probably fibrin deposits on the red cell, which became detached. Perhaps they are degeneration products extruded from the cell. Brownian movement gives them the appearance of true motility and they may readily be mistaken for leptospiræ and lead to mistakes as we saw in Gibraltar in 1944. The fallacies of examining wet films by dark ground render such methods of no practical value.

Sea-sickness Remedies

In preparing for combined operations it was found that the efficiency of the spearhead of an advance was likely to be rendered ineffective if the men had to traverse rough seas or be transported in gliders in stormy weather. The Medical Research Council in co-operation with the fighting services carried out investigations on remedies and it was found that hyoscine gr. 1/100 given one hour

be of the greatest value in a State Medical Service and would help to allay the suspicion that doctors have of administrators as a whole.

Since the Army assumes complete responsibility for all its members it can concentrate on preventive medicine in a way that has not been generally possible in civilian practice. Service responsibilities do not end with the patient's discharge from hospital, and the Army has been in a position to provide convalescent treatment, rehabilitation and controlled return to full activity. Army experience in these fields has obvious applications to civil practice.

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THE PROBLEM OF BACTERIAL VARIABILITY AND THE ORIGIN OF INFECTIOUS DISEASE *

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THE last decades have seen considerable progress in several branches of bacteriological research. I am grateful for the opportunity to discuss the advances made on two closely connected lines of investigation, one dealing with the variability of the pathogenic micro-organisms and its relation to pathology and epidemiology, the other concerned with the antigenic composition of the microbes and its relation to the specific antibody. Only a synthesis of the results from these researches can elucidate the complicated functions of the infective parasite and its interaction with the infected host, and give a sound basis to epidemiological conceptions.

In the infancy of the bacteriological era, when scientists found themselves for the first time confronted with the bewildering multiformity of microbes, there existed two schools of thought contending with each other in fierce opposition. The one, led by Ferdinand Cohn, professor of botany in Breslau, extended the familiar theory of systematic botany and zoology from the higher plants and animals to the unicellular organisms by postulating for them the same constancy of distinctly defined species. To these investigators the pivot and starting-point for the scientific recognition of bacteria and their chemical and pathogenic activities was the thesis that, to quote Cohn, " quite different genera of these organisms exist which always and only arise from germs of the same kind and differ by distinct development, distinct biological conditions and fermentative activities."

To be sure, the proof of this analogy thesis remained unobtainable as long as no irreproachable method of isolation was available. Thus it came about that for the time being the opposite camp of polymorphists prevailed, dominated by the publications of the German botanist Hallier (1866-68). Hallier, whose complicated devices of cultivation and isolation proved to be quite inadequate for their purpose, arrived at the startling conclusion that all the multifarious microbic features belong to one single elementary form, *Micrococcus*, which by virtue of boundless variability changes into the most different structures including moulds and algæ.

Hallier's scheme disastrously influenced and led astray the investigators of his days; still, in 1874, the Viennese surgeon and pathologist, Billroth, maintained that all the different micro-organisms

found in wound infections were descendants of a single species, a putrefying fungus, oddly named *Coccobacteria septica*.

The decisive turn to the theory of Ferdinand Cohn came from Robert Koch and his team by a spectacular advance in method, the invention of solid transparent media and the separation of pure cultures from single colonies. By this technique it became possible to isolate with regularity distinct species of microbes which maintained their morphological and biological properties with constancy. A consequence fundamental for the pathogenic micro-organisms sprang from this system of constant species, in accordance with Pasteur's theory of fermentation, namely, the famous thesis of Robert Koch, the first clause of the law of specificity: one single and constant microbial species belongs as causal agent to every infectious disease.

This conception of a distinctly defined constancy of bacterial species, moulded in opposition to the chaotic idea of the polymorphists and thus overpointed and too rigid, could in the course of time not withstand the ever-increasing mass of observations and experimental data. Time and again it became obvious that bacterial strains sub-cultured in the laboratory could more and more change their properties; there occurred instances of such variations which finally appeared to possess an even closer resemblance to another species than to their own parent strain. Moreover, the transformation of one well-defined pathogenic organism into another equally distinct infectious agent was occasionally claimed. To be sure, such extreme results have never stood the test of confirmation. It has to be emphasised that in all such experiments the absolute uniformity of the initial culture must be secured; irreproachable pure lines are an indispensable pre-requisite for conclusions from all variation experiments. The use of the single cell culture at the start is a valuable safeguard against the pitfall of an overlooked impurity. Such a precaution would have saved a pair of eminent workers not too long ago from their untenable and later withdrawn claim to have proved the identity of *Clostridium Welchii* and the motile Clostridium of malignant œdema.

A discussion of bacterial variability within the available space would be a dull enumeration, if an approach to completeness were attempted. The selection of representative examples will be more useful and has to start with a definition of the term. Not every change or deviation from the prototype, observed under changing conditions of growth in culture and in the infected tissues, is included under variation. Who would describe as true variations the physiological alterations of a plant or animal under the influence of transient stimuli, such as giant growth produced by overfeeding, anæmia by loss of blood, infection or toxin, bone deformities by lack of vitamin, etc.? All such temporary alterations belong to the normal morphological and functional cycle of the species and should be called physiological polymorphism.

Every bacteriologist is familiar with the differences in size of the

same strain under different conditions of growth ; some bacilli appear considerably smaller in the body of the host than in culture where they are again coarser on a solid medium than in broth.   Pfeiffer described the extreme enlargement of the normally minute influenza bacillus if grown on media containing certain toxic salts.   The development of the same bacillus in mucous colonies on saponin agar is known.   The inagglutinability of the typhoid bacillus from malachite green plates is not due to a variation, but to a temporary inhibition promptly removed with the removal of the cause.   The cultivation of flagellated bacilli on media containing phenol does not produce, at least not in the first cultures, a genuine non-flagellate variation, but only suppresses the formation of flagella as long as the inhibitory effect of the ectoplasmic damage by the disinfectant is maintained.

Only that alteration of a bacterial strain is termed variation which is observed in comparison with the parent strain under absolutely equal conditions of growth, and care has to be taken that the agent stimulating the rise of the alteration, for example, a toxic substance or a specific antiserum, has been completely eliminated, even from possible intra-cellular depots of storage.

A further point of importance is the stability or otherwise of a variation.   A variety may be permanently maintained, that is, may prove to be irreversible and definitive ; it may revert after longer or shorter periods into the initial type, or it may give rise to a further variation, that is, may prove to represent a transitory stage.   It seems to me a play with words to indulge in niceties of nomenclature, such as modification, dauermodification, mutation, derived from genetic studies on organisms with sexual propagation.   With a sexually multiplying micro-organisms the name variation covers the whole field, and supplementary information can be supplied by additions such as partial or total, reversible or irreversible, transitory or definitive.

The research on variability of bacteria started with the transformation of pathogenic organisms into their avirulent variants.   In the early eighties of the last century Pasteur found for two bacillary species methods of transformation into non-pathogenic or at least weakly virulent varieties.   Working with the bacillus of chicken cholera he laid by chance his hand on a culture several weeks old, no longer capable of producing a fatal infection, but still efficiently immunizing.   All subcultures of this attenuated strain, even if subcultured day by day, maintained the new character.   It seemed that a definitive variation of virulence had been obtained.   Shortly afterwards Pasteur succeeded in deliberately producing attenuated variants of the anthrax bacillus which also on subculture appeared to be irreversible.   The successful use of these cultures as vaccines in his famous immunization test at the farm Pouilly-le-Fort in May and June 1881 is a landmark in the history of bacteriology.

Soon, however, new facts came to light.   The attenuation of the new strains was not absolute.   Very young animals instead of becoming

immunized fell victim to a progressive and fatal infection. The strains recovered from the diseased tissues gradually increased in pathogenicity until the full virulence of the original strain was re-established. The variation had reverted.

This model experiment by Pasteur has found manifold confirmation with other micro-organisms. The variability of virulence in both directions, attenuation and restoration, seemed to be an established fact and served many bacteriologists as a basis for their ideas on the rise and the disappearance of epidemics. We have good reasons to be more critical in our conclusions to-day.

Innumerable unambiguous observations and experiments have proved the transformation of pathogens into avirulent saprophytes or attenuated varieties. Viruses are subject to similar alterations. The smallpox virus, most virulent for man, produces only the mild disease of cowpox in cattle. This vaccinia virus, when retransmitted to man, possesses but a diminished virulence, and has in more than one hundred years, even at the time of vaccination with human lymph, that is in direct propagation from man to man, never regained the original variola pathogenicity. I know that the genetic identification of variola and vaccinia has not been universally accepted. Undoubted, however, is the corresponding attenuation of the rabies virus from the high virulence of the *virus des rues* to the *virus fixe* used for vaccination.

Transformations *in vitro* of pathogen towards saprophyte are achieved with ease and regularity on many microbial species. Our experience is particularly abundant with pneumococci and streptococci.

Comprehensive investigations have been directed to those factors which produce such variations. Specific and non-specific influences are distinguished. Of *non-specific* factors, exposure to temperatures higher than $37°$ C., cultivation on non-optimal media or in the presence of toxic substances may be briefly mentioned. Still greater significance attaches to rapidly acting defence mechanisms in the body of an infected host, especially in certain organs. Lymph nodes invaded by the genuine toxic diphtheria bacillus yield after a short time completely and definitively transformed atoxic diphtheroids. Hæmolytic streptococci may be changed by certain tissues within two hours into the green-producing or viridans variety. The same effect has been achieved by cultivation in the presence of yeast cells. These antagonistic effects of living cells and tissues have nothing to do with specific antibodies and are obviously connected with the phenomenon of natural resistance. I have found a convincing demonstration of these tissue actions on pathogenic bacteria in two different methods—the addition of small fragments of fresh organs to broth and the direct inoculation on small excised pieces of mucous membranes. In both cases the efficacy depends on the survival of the tissue cells and is completely abolished, if the organ has been devitalised by steam.

Still more important and very effective in the regularity of their action are the three main groups of *specific* factors—the metabolic

products of the micro-organism itself, accumulating in an ageing culture; immune substances, antibodies, developing in the body of the infected host or added as immune serum to the culture medium; and the Twort-d'Herelle lysin, the bacteriophage. It is especially the use of immune serum, added to broth, which produces the avirulent variant with the greatest regularity and promptness.

The loss of virulence is rarely the sole change manifest in the modified strain. I mentioned the variation of toxic diphtheria bacilli into diphtheroids observed in infected lymph nodes. If some objection could be raised against the conclusiveness of the finding, the last doubt as to the derivation of such diphtheroids from the genuine Loeffler bacillus fell to the ground when Bernhardt and Paneth observed the same transformation *in vitro*, and I reproduced the change in active rabbit serum and on the surface of sterile pieces of a mucous membrane with single cell cultures. Moreover, I found that the variation passes through several stages; first, a variant with the cultural characteristics of the Hofmann bacillus was obtained, later this strain underwent the still more radical change to the xerosis type. So it appears that the two types of diphtheroids, formerly held to be independent species, are mere variants of the genuine diphtheria bacillus from which they differ so strikingly not only in toxicity but also morphologically, culturally, and in their fermentative activities. The routine work of the diagnostic bacteriological laboratory and the receivers of the reports should derive benefit from this unitary conception of the corynebacteria when confronted with those frequent occurrences of transitional cultures grown from later phases of the disease or from convalescents.

Another well-known example of combination of a virulence variation with other changes, morphological and physiological, is represented by the streptococcus. The most conspicuous alteration is here the loss of the hæmolytic enzyme and the appearance of methæmoglobin production; the colonies on blood agar are no longer surrounded by a hæmolysed zone, but produce a greenish area in the medium. There is no doubt whatsoever that hæmolytic streptococci can be transformed at will into green-producing or viridans strains by means of specific and non-specific factors. Viridans streptococci are mere saprophytes, almost ubiquitous on the respiratory and other mucous membranes. A causal rôle, however, in one serious disease is attributed to the type, since Schottmueller isolated for the first time the *Streptococcus viridans* or *mitior* from the blood of a patient with subacute endocarditis. Schottmueller held the opinion, shared by many others, that this viridans coccus in subacute endocarditis or sepsis lenta corresponds ætiologically and pathologically (in causation, mode of invasion, and infection) with the hæmolytic streptococcus in acute ulcerative endocarditis. I think this view is untenable and has in the light of modern transmutation research to be replaced by a very different conception, based mainly on the

rich experimental work by Morgenroth and his team. Is it con-
ceivable that a micro-organism invades the blood and infects the
heart valves where severe lesions and huge vegetations are produced,
and then exhibits complete avirulence not only in laboratory tests
but in the very patient where the frequent emboli never turn septic and
remain sterile on culture ? Much more convincing is Morgenroth's
thesis that the initial invader which injures the endocardial tissue is the
hæmolytic streptococcus. Subsequently the fate of both, patient and
microbe, is determined by the state of non-specific resistance or specific
semi-immunity of the host. If fully susceptible, then nothing is there
to check the micro-organism or to mitigate the destruction of the
infected tissue : consequence—ulcerative endocarditis, septic embolism
or multiple abscesses, innumerable hæmolytic streptococci, easily
cultivable, in the blood stream. If, on the other hand, a more resistant
or partially immune patient is quickly able to mobilise his defence
forces, an essentially different course of events follows—slowly
developing tissue lesions, predominantly hyperplastic, sterile embolism
and bland infarctions, the blood stream sterile or at long intervals
carrying a few cocci which are no longer virulent and hæmolytic, but
transformed to the avirulent and green-producing variety.

The most comprehensive and intimate knowledge of all the changes
concomitant with the variation from pathogen to saprophyte has
accrued from the study of pneumococci. It has been known for a
considerable time that the loss of virulence is regularly accompanied,
even characterised by the loss of the capsule. Avirulent pneumococci
are often resistant to bile and bile salts which dissolve the virulent
cocci. A phenomenon most characteristic of the virulence variation
has been discovered by Arkwright ; the appearance of the colony
changes from a uniform surface gloss to a mat dullness, from *smooth*
to *rough*. Many bacteria show the same transformation of the colony
from the S-form to the R-form when they turn from virulent to
avirulent. In broth and saline a corresponding change, studied by
De Kruif, is the change of the suspension from homogeneous to
granular. The fundamental difference in the chemical composition of
the variant is revealed by the change in the serological reactivity, the
loss of the type-specific antigen.

Only the analysis of the antigenic structure has elucidated the
essence of the variation process. The results of the investigations on
pneumococci have been confirmed in principle, though with character-
istic differences in detail, on a long line of other microbes, including
viruses, but the chapter of the pneumococci remains the most thoroughly
investigated and may serve here as pattern.

The first clue came from serological observations, made by Rufus
Cole in 1917. His co-workers at the Rockefeller Institute, mainly
Avery and Heidelberger, extended the research to chemical lines.
Zinsser and his co-workers at Harvard came independently and
simultaneously to the same fundamental results. The cell of the

virulent pneumococcus consists of a protein nucleus, the so-called P-substance, to which a carbohydrate, the C-substance, is linked. It is well known that the species of pneumococci has been subdivided by means of monovalent immune sera into characteristic serological types. The main types, I, II and III, the first discovered at the beginning of the century by Neufeld and Haendel, are responsible for 90 per cent. of all pneumonias, type III causing the most serious form of the disease. So far some 75 distinct types and subtypes have been differentiated. Now it was found that this type specificity depends on the difference of the C-substance, while the nucleo-proteid is common to all members of the species. The type-specific C-substance was chemically isolated and analysed as a polysaccharide, free from protein, differing for the different types in molecular composition, optical rotation, etc. The polysaccharide of type III could even be identified by Heidelberger and Goebel in its structural formula as an aldobionic acid. The purified carbohydrate is a white powder, readily soluble in water, and is still in minimal amounts (solutions of 1 in 5,000,000) specifically precipitated by the corresponding immune serum. Such serum, however, cannot be produced by immunisation with the isolated C-substance, but only by the intact C-P complex. In the nomenclature of Landsteiner the pure C-substance is, therefore, a " hapten," that is, a partial antigen or antigen residue, as Zinsser called it, acting specifically *in vitro* with the corresponding antibody, but incapable of stimulating the formation of the antibody. Space does not permit of a fuller account of the interesting details.

In contrast to the complex structure of the virulent type-specific pneumococcus the avirulent variant is free of carbohydrate, consisting only of the species-specific nucleo-proteid. That is the reason why all avirulent pneumococci, no matter from which of the different types the variation has been derived, are serologically and chemically identical. This statement is only applicable to the total variation. We shall see that intermediary stages in all possible transitional phases occur. Besides, I have, for the sake of clearness and shortness, somewhat simplified the situation; in fact, more than just two substances, C and P, are known to-day. This, then, is the essential process during the transformation of the pneumococcus from the pathogenic type to the avirulent variation, during the so-called " degradation " of the microbe—the loss of the carbohydrate portion in the antigenic mosaic.

I am not certain whether this generally accepted name of " degradation " for the loss of virulence is quite appropriate. There is an anthropocentric element in the term, the valuation of a biological standard in terms of aggression and bellicose proficiency. A microbe,. so less civilised than man, may not share the human glorification of living dangerously, it may prefer to live in peace and to be left in peace. A harmless parasite does not attack, nor is it counter-attacked ; it compromises with its host on the basis of a good neighbour policy,

profiting itself by the change from antagonism to symbiosis. Indeed, some saprophytes surpass their pathogenic kinsfolk in fermentative range and luxuriance under simple conditions of culture, indicating a step away from the precarious state of parasitism to the greater security of independent existence. Perhaps the variation from virulent to avirulent should rather be called promotion. We shall have to see a little later whether there is not more than just a joke in this consideration.

Now we have first to ask : What do we know of the variability in the opposite direction ; from avirulence to virulence, from saprophytism to pathogenicity ? It could be assumed that already the results of Pasteur's anthrax experiments and innumerable observations on old laboratory cultures have settled the question. Passage of an aged strain through a susceptible host is regarded as a classical procedure for the increase or re-establishment of virulence. This assumption, however, challenges the sharpest criticism of modern research. Such old cultures might consist, and more often than not do consist, of a mixed population, a few unaltered organisms being hidden in the avirulent crowd. The infected tissue acts like a filter by mere selection, simulating a true variation. This interpretation is supported by the experience that the enhancement of virulence by no means succeeds with all such old cultures and often enough defies even serial passages.

There is, of course, no doubt that a partial variation of any microbial feature may revert. Occasionally a hæmolytic streptococcus has been recovered from a pure line of viridans cocci or a paratyphoid bacillus in S-colonies from an avirulent R-strain.

The studies on pneumococci furnish again the most detailed information. When the loss of the C-substance is complete, no reversion of the degraded strain is achievable ; but where rudiments of the original structure have been preserved, the variability back to the parental virulence persists ; the rehabilitation can be produced at will by means of specific and non-specific factors, again in the easiest way by the addition of immune serum, this time anti-P, to a broth culture. Moreover, it has been shown by an ingenious method that the rehabilitation is not necessarily tied to the track paved by the preceding degradation, but can be deliberately guided, shunted as it were ; a degraded variant of *one* type can be rehabilitated to a virulent strain of *another* type.

We owe this sensational discovery to F. Griffith (1928), whose untimely death in the London blitz of 1941 deprived the bacteriological community of one of its finest members. Neufeld and Levinthal, generously initiated into the results before publication, were privileged to carry out the first series of confirmatory experiments and to remove the last doubt in Griffith's conclusions by the use of single cell cultures. Later, Dawson in the U.S.A. succeeded in reproducing the same variations with the method of Griffith *in vitro*, a great achievement.

The method of Griffith is this : the living avirulent strain is propagated in contact with a large amount of heat-killed virulent cocci. The killed material acts as a foodstuff for the multiplying cells of the P-strain and provides a specific raw material for the synthesis of a P-C structure. The direction of this synthesis is determined by the chemical composition of the food : if it consists of P-C^1, that is, killed cocci of the type I, then the avirulent coccus rebuilds itself to a type I ; if the food consists of the dead body substance P-C^2 or P-C^3, the corresponding type is formed, irrespective of the original type from which the avirulent variant has been derived. The latest progress (1944) in this transformation of type has been recorded by Avery, MacLeod and McCarty, who produced a type III from the rough variant of type II by feeding with a pure chemical substance, namely with deoxyribonucleic acid, prepared from type III.

Thus Griffith has given us a systematic technique for the transformation of one virulent type into another via the degraded variety. Griffith has emphasised that this avirulent variant must not be deprived of its original type character in too mild a degree, otherwise it always rebuilds the original form with the material from any type. On the other hand, Neufeld and I have shown that the avirulent strain must not be too completely split up, not degraded to pure P, otherwise it has definitely lost the capacity of any rehabilitation. The original view, however, that the heat-killed material simply acts as a " pabulum " for the R-strain had to be abandoned in the light of later investigations, although the nature of the transforming principle which induces the change in a specific way still remains obscure.

It is most interesting that the illuminating discovery by Griffith has been paralleled in the virus field. I shall describe the story in some detail because it brings forcibly home the fact that viruses are subject to the same laws of variation as the larger microbes with one difference. The degraded variety is not completely devoid of pathogenicity, but still causes recognisable lesions, though of much milder character. That is chiefly due to our technical imperfection. We are methodologically handicapped by the obvious difficulty of how to detect a completely avirulent virus. Cultivation and direct microscopical observation are still in their infancy, and as soon as a virus loses all pathogenicity, it escapes the classical way of demonstration by animal inoculation and slips unnoticed through our fingers.

In 1898 Sanarelli discovered a very malignant disease in cotton-tail rabbits, the almost always fatal myxomatosis. The disease which occurs only in South America is exceedingly contagious and is transmitted through the air. Rabbits alone are susceptible. The infectious agent is a virus ; the characteristic lesions are tumours mainly composed of a gelatinous mass. The rare convalescents are solidly immune. In 1937 Hurst succeeded in the deliberate transformation of the virus into an attenuated variant which only causes

a mild disease with benign, non-myxomatous swellings subsiding after some days.

In 1932 Shope found also in cotton-tail rabbits an infectious fibroma, a virus disease of benign character. The convalescents are immune. Very soon Shope became aware of the fact that fibroma convalescents are partially immune to myxomatosis. The illuminating serological relations between the two viruses, studied in the U.S.A. and in this country, must be omitted here, but they warrant the conclusion that the virus of the Shope fibroma is not a separate species, but only a degraded variation of the myxoma virus. And the chain was clenched in 1936 by Berry and Dedrick who rehabilitated the benign virus of Shope's fibroma by the Griffith technique, that is, by means of heat-killed myxoma virus, to the malignant agent of myxomatosis.

It is, then, clear that the research on microbial variability critically sifted has not shaken the pillars of the fundamental law of constancy. No claim to transformation of pure saprophytes into infectious agents or of one pathogenic species into another has ever been verified. However, the firm boundaries of the species such as they once appeared to their discoverers have become more fluctuant on many points. The rigid definition which demands from all the representatives of a species and their descendants the sum total of exactly the same properties has been replaced by a more liberal conception which concedes to the aberrations from the prototype an equal right within the framework of the species. The constancy of the species is preserved by the stability of what Sir Frederick Andrewes has called the " centre of variation," around which and tied to which the variants scatter. A metamorphosis from one genuine species to another genuine species is no less unknown to the world of microbes than to the system of higher plants and animals, where the race-forming effects of variabilty in the display of natural factors as well as in the hand of the deliberate breeder possess so conspicuous an importance.

Equally unshaken remains the solid structure of the law of specificity, but the new more fluid conception of constancy has led to a refinement of definiton. Not just a microbial species is ætiologically associated with an infectious disease, but only the virulent type with its biological characteristics.

Even the second, Behring's clause of the law of specificity, has been affected by the revaluation of definitions—the defence forces, antibodies and immunity, are strictly specific to the virulent form of the causative antigen. Active and passive immunization, vaccination and serotherapy, are in many infectious diseases adequate only if specifically corresponding to the type of the germ. A lobar pneumonia caused by type I responds only to treatment with an anti-I serum. The striking effectiveness of serotherapy against the toxins of botulinus and gas gangrene depends on the choice of the correct type of antitoxin, or if the type of toxin is unknown in a given case, on the use of poly-

valent serum. The favourable results of Danish workers in their immunization campaign against whooping cough could not be reproduced until *pertussis* strains in the virulent form, the so-called phase I, were employed in the preparation of the vaccines.

Finally, the question arises: Have the results of modern research on variability fertilised the theses and hypotheses of epidemiology, the ideas on the rise and decline of infectious disease? Long ago Robert Koch, watching the ups and downs of a great cholera epidemic in Egypt, explained the subsiding of the evil by a variation of the infectious agent. He said: " This observation can only be explained by the assumption that towards the end of the epidemic the contagion suffers some loss of efficacy or at least becomes unstable in its action." Twenty-five years ago it was generally assumed that the decline and disappearance of an epidemic in a population where still many individuals remain susceptible is only explicable by a variation of the infectious agent, by an attenuation of virulence.

However, a great surprise sprang from the experimental studies of epidemics carried out under natural conditions in the laboratory. The epoch-making work by Topley and his co-workers in England and by Simon Flexner and his team, especially Webster, in the U.S.A., has necessitated a revision of views, at least for the group of diseases with relatively stable germs. It has been found that the disappearance of an enteric epidemic can occur, without any variation of the causal micro-organism, only by changes in the susceptibility of the host population and by the quantity of the disseminated contagion. Moreover, the important fact has come to light that the flare-up of the disease and the spread to the survivors of the first outbreak is achievable by a change in the composition of the infected population only, by the mere arrival of newcomers, again without a variation of the micro-organism.

It is true that the situation might be somewhat different in respiratory diseases caused by less stable microbes. In one of his latest reviews on influenza C. H. Andrewes, one of the co-discoverers of the influenza virus, concludes from his observations during ten years and from epidemiological considerations that in the interepidemic periods the virus must persist in carriers and mild cases in a variation of low virulence, reverting to higher pathogenicity at the time of minor epidemic waves and to maximal virulence at longer intervals (forty to fifty years) when the great pandemics ravage the globe. I am inclined to subscribe to this view the more as I have, twenty-five years ago, formulated the same conception and offered an explanation for the increase and restoration of virulence. However, even in these epidemic diseases the degree of susceptibility or immunity in the human population and the quantity of the disseminated virus presumably play a greater part in the shaping of the outbreaks than the microbial variability. It is clear that even the extinction of an epidemic or the attenuation of its severity does not make the assumption of a virulence

variation indispensable, although the variability of many microbes in this direction is warranted by countless observations and exact experiments.

The flare-up of an epidemic could be partly caused or at least accompanied by a reversion of the previously attenuated microbe, again an experimentally proved possibility.

No datum, however, has issued from the research on variability which possibly could justify the conjecture that infectious disease arises by the gradual or sudden transformation of pure saprophytes into pathogens, by the pathogenisation of an avirulent commensal. True, if no alternative were available to explain the rise of a pathogenic micro-organism, then such a working hypothesis may be permissible as a logical postulate, so far unsupported by proof. But it is not necessary, and just logical considerations render it even improbable. The saprophyte lives with its host in perfect peace. A variation into a pathogenic aggressor creates at once an open feud between parasite and host. This state of war imperils not only the carrier of the infection, but much more vitally the microbe which has to pay with its existence for the contest in each case ; if the patient succumbs, then the parasite, too, perishes with its provider. If the patient prevails, then the germ succumbs. The flight into fresh hosts, a mere respite, saves but a few. Only the transformation into the non-pathogenic variety spells definitive salvation of the bacterial species, the uncontested settlement in the refuge of peaceable symbiosis. The saprophytic settler no longer stands in belligerent interaction with the carrier whose defence forces and antibodies against the pathogenic ancestor do not hit the altered antigen of the avirulent offspring.

Symbiosis means equilibrium to which the struggle during the period of pathogenicity forcibly tends. A stimulus out of this well-balanced stability towards the instability of pathogenicity is not easily imaginable. It is true that the science of genetics has acquainted us with desultory changes arising without purpose and direction, but the unsuitable mutation has little chance of survival and a high rate of rapid elimination.

Thus the collection of data from research as well as pure deduction militate against the hypothesis that micro-organisms pathogenic for man have arisen from human saprophytes by variation. On the other hand, no difficulty attends the effort to elucidate the origin of infectious disease by an analysis centred not on the parasite but on the host—a microbial species, free living or as harmless parasite of some host leads an existence of perfect saprophytism, until a chance transmission to a sensitive genus or race affords the first opportunity to deploy a pathogenic capacity already inherent but never before manifest for lack of a suitable object. I beg leave to expound my argument by a simile. Meadows and swampy grounds are covered with mushrooms. There they have luxuriated for ages, prior to the higher plants and animals, in many genera and species, and the sun

has shone over the good and the evil. Indeed, there was no good or evil, no differentiation between edible and poisonous as long as there was no suitable consumer for the discriminating test. Late, very late in their day, when a mere chance contact with man furnished the first opportunity for manifestation, a victim's costly experience revealed the potential toxicity of certain toadstools.

Many spirilla and vibrios grow in stagnant pools or as saprophytes in the intestines of mammals ; one of them, the cholera vibrio became a pathogenic microbe not by variation but by a change of habitat, when it met for the first time with susceptible man. Spirochætes thrive in ticks, harmless for their hosts, until infected man supplies the unaltered parasite with the first opportunity for the demonstration of a deleterious property. Margarete Zuelzer detected on Sumatra in a region of the jungle never touched by human beings a water leptospira which, in infecting native members of her expeditionary troupe, revealed its identity with the microbe of Weil's disease. Moreover, this *Leptospira icterohæmorrhagica* occurs as a saprophyte in the resistant water rat and acquires its dangerous character not by variation, but by migration to the highly sensitive human host. Pasteur observed that the bacilli of chicken cholera, the causal agents of fatal infections in hen and rabbit, can be carried by guinea-pigs as almost avirulent saprophytes. He commented : " Chickens or rabbits, living in contact with such guinea-pigs, could suddenly fall ill and perish, without any apparent disturbance in the health of the guinea-pigs."

Our own generation has witnessed the creation, nay, the manufacture of an entirely new severe infectious disease, caused by a virus which is almost ubiquitous in its natural host and practically a mere saprophyte producing trivial lesions only in damaged skin and mucous membrane. I mean the herpes virus, intensely pathogenic for the rabbit which suffers from a spreading keratitis or fatal encephalitis. Doerr (Basle) once stressed the phylogenetic inexplicability, the lack of a " historic cause " for this pathogenic adaptation of the herpes virus to the rabbit.

The saprophytes of one animal genus and the pathogenic organisms of the new host are identical in their properties but differ in their effects ; the alteration of effect is due not to a variation of the microbe but to its migration, to the change of host.

Do we not meet day by day with similar pathogenisations within the confine of the same host system ? The saprophyte of one resistant region grows pathogenic if transmitted to a sensitive organ of the same body. The harmless commensal of our bowels, *B. coli*, is pathogenic in the bladder and in the uterus after parturition ; *Clostridium Welchii*, irresistible destroyer of muscular tissue, is a harmless and common saprophyte on intestinal and genital mucous membranes. Such migrations from resistant to sensitive regions of the same carrier would then be the second possibility for the origin of pathogenicity.

There is a third and last source of a pathogenic microbe, perhaps

one of particular significance in the history of infectious disease—
pathogenisation without any change of habitat by change of
resistance in the carrier. This change has an individual and a racial
aspect.

Tissues which under normal conditions are unharmed by their
saprophytic flora fall, after injury and in diminished resistance, victim
to commensals of their own household running wild. The way for
the (quasi) " pathogenic saprophyte " may be paved by a primary
infection or other local disease such as cancer. Influenza, tuberculosis,
gonorrhœa create a *locus minoris resistentiæ* for a secondary invader
such as viridans streptococci, putrefying bacilli, diphtheroids. Or a
systemic damage by malnutrition, overstrain, etc., may break the
chains on which the carrier holds his avirulent commensals.

Still greater significance attaches to the racial changes which are
the heritage of civilised man. I am far from thinking that the bearer
of civilisation is as a whole physically inferior to his primitive fore-
bears ; I even believe that he surpasses them in stamina. On the
other hand, the resistance of some body regions, especially the
respiratory and perhaps the intestinal tract, has deteriorated. The
cradle of mankind was situated in lands with mild and kind conditions
for his existence, but man has conquered the world. He has managed
to adapt himself to harder surroundings, he has learned to live even
in the harshest climates, for example, in those high valleys of
Switzerland with nine months of winter and three months of cold.
However, he has to pay the price for such luxuries. One telling
example may stand for many.

Diphtheria is practically unknown in the tropics. So it has been
assumed for a long time that the Loeffler bacillus does not occur or
survive in those parts of the earth. Our views had to be fundamentally
revised when examinations of the native population by means of the
Schick test revealed the same circumstances as in countries where the
disease is rife. Positive in children, the ratio of negativeness increases
proportionally to age, indicating an infection without disease, an
infection inapparante. It will be remembered that in civilised countries
also the incidence of healthy carriers is very high. The number of
healthy carriers by far exceeds the number of frank cases of the
disease. Man is capable of dealing with small amounts of diphtheria
toxin without illness. If, however, the invading micro-organism
abundantly multiplies on mucous membranes of diminished resistance,
the production of toxin outruns the slowly developing immunization
and frank diphtheria is the end result of the host's altered constitution.

To sum up, the results of modern research on bacterial variability
exert little influence on epidemiology. No doubt pathogenicity arises
out of saprophytic existence ; the microbe, however, does not acquire
pathogenic power by a variation of properties, but by a change of
opportunity for action in a changed habitat. The virulence, appearing
as a new characteristic, depends on the susceptibility of a new or

newly transformed host. The increase of value is relative, not absolute. The origin of infectious disease and epidemic is due to the huge migration in the world of microbes and to the variability of the human host.

That, however, is a different story, not a subject of microbiological research and a topic of a bacteriological lecture. It will, I suppose, form an important part in the new or renewed branch of biological science called social medicine, employing statistical analysis and experimental methods on lines paved by the pioneer work of Topley and Webster, with the focus of attention fixed on man (and mice), not on microbe.

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RHEUMATIC ENCEPHALOPATHY

By DUNCAN LEYS

PSYCHOTIC symptoms of all degrees of severity are seen in chorea, from those scarcely to be distinguished from the uneasiness of a self-conscious child through all grades of emotional disturbance to chorea insaniens or hypomania. Disorientation and hallucination such as might be described as delirium, and sometimes semi-coma occur. In general the mental symptoms are parallel to the choreic motor symptoms, improving as involuntary movement, paresis, hypotonia, and diminished or absent tendon jerks are replaced by normal mechanisms. During the months of December 1943 to March 1944, however, I observed three girls with rheumatism or chorea, all at or shortly past puberty, with an unusual type of psychosis. Two of these patients were seen by a consulting psychiatrist, who diagnosed them without hesitation as schizophrenic. All recovered sufficiently to resume active life and are in good health one year after the illness. A description of these cases is given below.

CASE I.—Elizabeth M., aged 14. She was admitted to hospital on 26.12.43. She is the eldest of a family of four; one brother has been deaf and dumb since meningitis, aged two. Measles and whooping cough in infancy. Scarlet fever, aged six. Menarche, August 1943, but she did not menstruate again until mid-December.

20.11.43. Sore throat, and onset of typical rheumatic arthritis, 3.12.43. On 7.12.43 involuntary movements noticed, which were painful. 11.12.43 erythematous rash (described as large red areas on shoulder, knee and jaw, which persisted for about ten days). Nose bleeding twice during the two weeks preceding admission. Gradually became indifferent to surroundings, had fits of screaming and crying, spoke rarely and seemed hallucinated.

Examination: A tall girl. Rather emaciated. Well-marked puberty changes. Typical and fairly severe choreic movement with hypotonia, complete absence of tendon jerks in arms, and delayed sustained response in legs. All voluntary movements extremely feeble. Babinski negative. Heart probably enlarged; apical systolic murmur conducted a short way towards axilla, blood pressure, 115/80.

31.12.43. Exceedingly restless in spite of sedatives; sleeps only three or four hours in the twenty-four. Epistaxis. Spinal fluid pressure probably not high (no reading because of restlessness and undesirability of using anæsthetic). No increase in cells; protein, 25 mgms. per cent.; no globulin; chlorides, 748 mgms. per cent. Colloidal gold, 000,000,000,00. Wassermann Reaction negative. 1.1.44. In spite of adequate fluid intake, urinary output less than six ounces in twenty-four hours, but this period of oliguria followed by incontinence when impossible to get measure of output. At this time, febrile, and remained so during the next two weeks.

During ensuing weeks behaviour increasingly schizophrenic. She held no communication with doctors or nurses, resisted in a passive sort of way efforts to keep her clean, and became completely incontinent. She would

not feed herself and refused to swallow. It was judged that no definite dysphagia was present. Catheter feeding was resorted to. Choreic movements much less in evidence. Particularly striking was the attitudinisation typical of dementia præcox with catatonia.

22.2.44. Seen by consulting psychiatrist, who considered this a case of schizophrenia. After this consultation transfer to the mental hospital was arranged, but at the request of the ward sister, who was optimistic about her, this was postponed for three or four days. Her optimism was fully justified, and such rapid improvement now began that by 3.3.44 it was noted that " her behaviour would not now strike one as eccentric." The picture was one of a gradual awakening and increasing interest in surroundings interrupted by periods when the old catatonic gestures would occupy her for a few minutes at a time. On 17.3.44 she was discharged to her own home one hundred miles away, able to walk and to travel by train. Her heart condition was unaltered.

She was seen again on 13.7.44 when her family reported that she had tended to trail her left leg for a time after returning home, and that there had been occasional difficulty with speech. Amenorrhœa continued until July. At examination she was lively and cheerful. No choreic movement was seen, but there was some hypotonia and depression of tendon jerks in the arms.

On 11.8.44 she was readmitted to hospital at the request of her doctor when dynamometer readings, right 75, left 70, were noted as compared with right 55, left 40, on 7.3.44. Her sedimentation rate was 7 millimeters. Definite but slight choreic movement was noted. She was kept in hospital for a week and then was discharged to her home. An X-ray of chest showed a slight " mitralisation " of the heart. During the period 27.2.43 to 18.9.44 (approximately six months) she gained twenty-four pounds in weight.

CASE 2.—Mary M., aged 21. The eldest of three children. Described as always lively and sociable, not moody or reticent, but rather sensitive. She was considered by a recent employer (domestic) to have been rather nervous and timid. Aged 14, measles and scarlet fever.

In January 1944 an acute febrile attack was followed almost immediately by typical rheumatic arthritis. She was put to bed, the arthritis quickly subsided, and she was reckoned convalescent by her doctor when, on 7.3.44, she quite abruptly began to have 'fits of weeping, seemed depressed, spoke in vague terms about religion and guilt, and then became first reticent, then unco-operative, and finally refused to have any communication. The symptoms varied somewhat from day to day, and when first seen by me on 16.3.44 she was amiable and co-operative at the beginning of the examination and completely antagonistic before the end of it.

Admitted to hospital on 18.3.44, she regarded everyone with suspicion, and would not reply to any questions or indicate her wants. No choreic movement or paresis was observed. The heart rate was 100. Her blood pressure was 130/90 and an apical systolic murmur suggestive of a mitral lesion was heard. No nodules were seen. Sedimentation rate was 20 millimeters (Westergren one hour). Shortly after this she became restless with incoherent muttering, disoriented, and refused food. Chloretone and rectal paraldehyde were used as sedatives, and her condition demanded intravenous fluid and duodenal tube feeding. 21.3.44. Tendon jerks in the arms, all present on admission, had disappeared. Abdominal reflexes absent also. Plantar responses, left definitely flexor, right indefinite. Spinal fluid pressure

not measured because of restlessness. Protein 35 mgms. per cent.; no globulin; no increase in cells. Wassermann Reaction negative. Colloidal Gold, ooo,ooo,ooo,o. Hæmoglobin, 90 per cent. White blood cells, 14,000.

On the theory that the cerebral symptoms might be due to œdema, 100 c.c. of 20 per cent. sucrose solution were given intravenously without apparent influence on the condition. During the next month, her symptoms were much the same, with alternating periods of coma and restlessness, retention and incontinence. Her spinal fluid pressure on 17.4.44 was 2 centimeters, rising to 8 centimeters with jugular compression.

On 11.5.44, since no signs of improvement were noted she was seen by the consulting psychiatrist, who diagnosed schizophrenia, and was then transferred to the mental hospital under his care. On 3.6.44, there being still no improvement, she was given convulsive therapy. During the ensuing weeks there was slow, quite steady improvement, and she was discharged to her home apparently recovered on 27.9.44.

CASE 3.—Kathleen P., aged 14. She is the third of four children, a clever child, well ahead of contemporaries, and intending to study medicine; athletic and described as of happy disposition. Pneumonia aged 12. Menarche, March 1943.

In October 1943 some loss of emotional control was noted, and movements which were first thought to be an imitation of tics displayed by a girl friend who was staying in the house. More or less simultaneously with these movements, she began to complain of intermittent pain in her limbs. Later, difficulty in performing fine movements with left hand was noted, together with weakness of the left arm and leg. She was admitted to hospital on 20.12.43.

Examination : A tall girl. Good nutrition. Pronounced puberty changes. Heart not obviously enlarged, but loud systolic murmur heard at apex and near left border of sternum. Blood pressure 115/65. Obvious choreic movement. Much paresis, but tendon jerks in arms still present and exaggerated in legs. Doubtful plantar responses. Dynamometer readings, right 70, left 60. Athetoid position of hands. Abdominal reflexes easily tired. Sedimentation rate 5 millimeters (Westergren, one hour). 31.12.43. Movements much less obvious, but hypotonia extreme and complete loss of tendon jerks in arms. Dynamometer readings, right 15, left 45. Rather emotional.

She now lapsed rather rapidly into a condition of almost complete coma. Choreic movements ceased. There was profound hypotonia with complete absence of tendon jerks. She became speechless. She could be roused with difficulty, was fed very laboriously by spoon, and became completely incontinent of urine. Her spinal fluid pressure was 24 centimeters, rising to 30 centimeters with jugular compression. Protein, 30 mgms. per cent.; no increase in cells ; no globulin ; chlorides, 737 mgms. per cent. Wassermann Reaction negative. After remaining in this condition for about ten days, a very rapid improvement was noted. On 25.1.44 dynamometer readings, right 65, left 70. She sat up, began to talk and to take an active interest in her surroundings. On 28.2.44 she was so much recovered that she was discharged to her own home. No definite signs were noted then in the heart and the X-ray was normal.

She was seen again on 26.5.44. She was reported to have reproduced, after leaving hospital, all the signs of an active chorea. This relapse had preceded the news of the loss of her brother on service, but seemed to have

been aggravated by it. She was last seen on 11.8.44, in good health, with no signs of chorea. The heart was not obviously enlarged, but an apical systolic murmur was heard and a doubtful diastolic. Her blood pressure was 120/90. Her weight had increased by fifteen pounds in four months.

DISCUSSION

Acute rheumatism is endemic in Great Britain. It has familial characters for which studies suggest a two-fold basis, hereditary (*i.e.* it occurs among sibs not necessarily in physical contact with the patient), and epidemic (*i.e.* occurring within the household in such a way as to suggest contact infection). Other considerations suggesting a potential epidemic character are :

(*a*) Its geographical distribution : city populations more susceptible, but latterly in Great Britain a tendency for rural populations to suffer more heavily (? the effect of population movement in war) ; other things being equal, a diminished frequency from north to south.

(*b*) The association of rheumatism with poverty (rheumatic conditions several times more common among elementary school children than among children in private schools ; an uncommon disease in well-managed institutions, orphanages, etc.).

(*c*) Its seasonal variation with increase in winter months and peak at the period of lowest sunshine.

(*d*) Annual variations in frequency.

In the Scottish Highlands it has been a relatively rare disease, a fact which is forcibly brought home to one who, like myself, has migrated from a large city. Among 8430 patients seen in hospital during the six years preceding the writing of this paper, in consultation with doctors in the Highlands and Islands service, and in private practice, there have been thirty-five with acute rheumatism or chorea (acute rheumatoid arthritis is excluded, as are also all doubtful diagnoses and all cases of carditis not seen in the acute stage of infection).

From time to time everyone in clinical practice observes, within a relatively short space of time, more than one example of a rare disease process. Occasionally the explanation lies in the fact that awareness has been sufficiently increased by the first observation to make possible the second or third, an observation which might otherwise have been missed. This is, however, only a likely explanation if the symptoms are of a nebulous kind, confusing in their association, or only recently described.
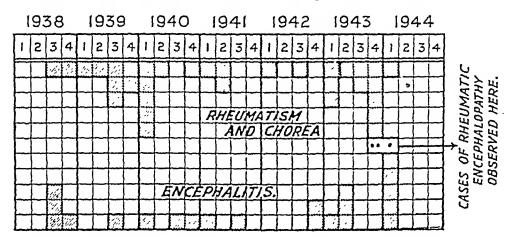
Such an explanation does not account for the failure to observe schizophrenia in rheumatism before, since its outstanding characters of withdrawnness, negativism, catatonia and coma, are not easily to be mistaken. The odds against the conjunction of the cases being fortuitous must be extremely high. It is possibly significant that the year preceding the appearance of these cases of rheumatic encephalitis was for this area not only one with a high rheumatic rate, but also a year in which meningo-encephalitis was prevalent.

TABLE

Encephalitis (including lymphocytic meningitis) formed the following percentage of my cases in the years 1938-1944

Year.	1938-39.	1939-40.	1940-41.	1941-42.	1942-43.	1943-44.
Total cases .	823	1251	1602	1456	1727	1669
Encephalitis .	5	3	3	3	9	1
Per cent. . .	0·62	0·25	0·19	0·2	0·56	0·06
Rh. and Chorea .	4	12	4	2	3	10
Per cent. . .	0·49	0·93	0·25	0·14	0·19	0·56

The seasonal incidence of these two diagnoses is shown below.

I suggest that these three girls suffered an illness of this type because their puberty coincided with a period not only of prevalence of rheumatism, but also of prevalence or " enhancement " of pathogenic neurotropic virus. The two latter factors may, of course, be identical. Rheumatic psychosis of various types, including schizophrenia, has been described by neurologists or psychiatrists in studies of psychosis or encephalitis, but does not seem to have been remarked by pædiatricians. Chorea or rheumatic encephalopathy would appear to be very much modified by the age, sex, constitution and experience of the victim, and very possibly by endocrine or biochemical factors, since it has a noteworthy frequency during puberty and pregnancy, and is rarely if ever observed in men. Alternatively, the rheumatic infection can be regarded as a precipitator, under favourable circumstances, of an emotional crisis or tangle which was latent, and which may be perpetuated. Neal (1942) describes cases of chorea with cataleptic features and a picture " resembling schizophrenia." Such cases, she says, show athetosis, loss of tendon jerks, aphasia, catatonia, hypotonia, dysphagia, and coma. Kinnier Wilson (1940) says that " all symptoms of a toxic psychosis may be evident. Cases of this sort are seen mostly in adolescence or adults. Depression and paranoid features are unusual." Winkelman and Eckel (1932) describe cases

of encephalopathy occurring in acute rheumatism with, they believe, a basis in endarteritis and œdema. Coombs (1912) considered " cerebral rheumatism " an entity. Bruetsch (1944) is another psychiatrist impressed by the relationship of rheumatic infection to psychosis. He approaches the subject from another angle, *i.e.* an analysis of the incidence of rheumatic heart disease in autopsies on patients dying in a mental hospital. The over-all incidence was 5 per cent. and among schizophrenics, 9 per cent., as compared with 1 per cent. estimated rheumatic heart disease in the general population. Even allowing for the fact that fewer cases will be observed in life than discovered at post-mortem, this elevated incidence of heart disease amongst psychotics must be considered definitely important. He also found clinical evidence of rheumatism in 8·1 per cent. of new female admissions, but in only 2·6 per cent. of new males. He considers that psychosis may appear months or years after clinical rheumatism, and that it is due to a continuing infection.

The well-known recurrence of chorea in certain women in pregnancy lends some support to this idea. We are unfortunately without any exact criteria in clinical pathology which could determine the correctness or falseness of the view that the encephalopathy of chorea or acute rheumatism is a frequent cause of schizophrenia, but it seems worth while to bear in mind the possibility that emotional difficulties and even grave psychosis may follow rheumatic fever.

To entertain this idea one need not be committed to any completely materialistic or histiocytic conception of rheumatic encephalopathy. D. W. Winnicott (1945) considers that as the mind depends directly on the brain it is bound to be affected by physical brain disease, but that it is by no means true to say that mental disease needs brain disease. He thinks that when the brain is affected by inflammation, degeneration, tumour, etc., the resulting mental state is very much determined in quality by the previous mental set-up of the patient. On this conception, mental disorder in chorea, if it occurs, will be of a kind which the patient would be likely to show under other forms of stress.

The symptoms are described of encephalopathy occurring in three girls with acute rheumatism : two had a psychosis indistinguishable from schizophrenia. All recovered. The subject of rheumatic encephalopathy and its relationship to psychosis is briefly discussed.

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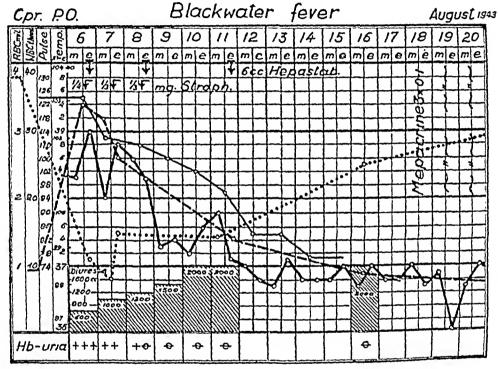
A CASE OF BLACKWATER FEVER
OBSERVED IN BRITAIN

By HENRYK DLUGOSZ, M.D. Lwów

BLACKWATER FEVER is often encountered in countries where subtertian malaria is endemic. Under the greatly changed conditions brought about by the world war and the increased facilities for the aerial transmission of disease, it would be wise for doctors practising in more moderate climates to be on the outlook for similar or other manifestations of tropical diseases. This particular case of blackwater fever provides the obvious example that such suggestion is right.

Fig. I.

On 6th August 1943 the patient, aged twenty-nine years, was admitted to hospital. Four days previously, 2nd August, following exercise, he had complained of feeling weak ; he had a cough and his temperature became slightly elevated. He consulted his doctor who diagnosed bronchitis and prescribed the usual treatment. On 5th August he collapsed after the onset of sudden severe abdominal pain. Camphor and caffeine injection produced a slight improvement in his condition. On 6th August the morning temperature reached 102° F. (38·8° C.), and as his general condition was now rather alarming, he was brought to hospital with a diagnosis of broncho-pneumonia.

On admission the patient gave the impression of a very sleepy or tired man. His temperature was now 101° F. (38·3° C.) (Fig. I). The

TABLE I

The Comparison of the Blood Examinations

Date	W.B.C.	R.B.C. Millions	Hb per cent	C.I.	Neutrophil Myelocytes	Young Cells	Staff	Segmented	Eosinophils	Basophils	Lymphocytes	Monocytes	Plasma Cells	Megaloblasts	Normoblasts	Reticulocytes Per Cent	Platelets	Remarks
6.8.43	34,400	1·10	30	1·36	0·6	2·8	14·6	50·6	0	0·4	13·0	14·6	3·4	2·	5 for 500 W.C.	...	314,000	1 pint of plasma
7.8.43	32,400	·82	31	1·9	0·4	1·6	18·4	45·2	0	0·4	23·2	8·8	2·0	3	4 for 250 W.C.	9·4	952,000	Before transfusion
7.8.43	27,900	1·56	44	1·4	2·0	10·7	46·0	2·3	28·0	0·3	8·7	2·0	0	0	9 for 300 W.C.	...	...	After transfusion of 1 pint of stored blood
11.8.43	15,000	1·53	41	1·3	2·4	17·6	55·6	2·0	15·2	0	6·0	1·2	0	6	0 for 250 W.C.	...	...	Prominent anisocytosis, many microcytes and poikilocytes. Polychromasia
12.8.43	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Haemolysis begins at 0·42 per cent. Complete at 0·34 per cent. Distinct anisocytosis; many microcytes and poikilocytes. Single parasites of benign tertian
16.8.43	9,900	2·45	57	1·1	0·4	9·6	49·2	1·6	33·6	0·8	4·0	0·8	0	0	11·8	...	...	Marked anisocytosis. Single parasites
30.8.43	4,900	3·85	78	1·0	1·2	51·6	1·6	1·2	36·4	7·6	0·4	0	0	0	...	1·2	192,500	Marked anisocytosis. No malaria parasites
11.9.43	8,900	4·96	94	0·95	2·0	64·8	0·4	0·8	23·2	7·6	0	0	0	0	...	...	...	Anisocytosis insignificant
7.2.44	...	5·10	100	0·98	...	...	...	...	...	...	...	...	...	...	...	...	...	...

skin was very pale and rather yellow in colour. Lips and ears had a cyanotic hue. There was no evidence of hæmorrhage, superficial or from mucous membranes. Over the base of the right lung breath sounds were harsh. Fine crepitant and consonant râles could be heard. Heart sounds were normal. The pulse, 124 per minute, was rhythmic but very soft. The liver was enlarged two finger-breadths below the costal margin and was tender on palpation. The spleen was not palpable. The abdomen presented no abnormality. There were no signs of œdema of the legs.

Before admission micturition was normal and the patient did not observe the colour of the urine. The first hospital specimen was 290 c.c. in amount and of a dark turbid colour somewhat resembling water rinsed from tainted meat. On standing a dark sediment could be seen. The specific gravity of the urine was 1014, the reaction acid. Albumen was present (4 per litre Esbach). Tests for sugar were negative. Microscopic examination of the sediment revealed per high-power field : 4-6 white cells and 5-10 red cells, masses of brown detritus, some granular and single epithelial casts. The benzidine reaction with the sediment was strongly positive.

Blood examination : W.B.C., 34,400 per c.mm. ; R.B.C., 1,100,000 per c.mm. ; Hb, 30 per cent. The white cells analysis gave the result enumerated in Table I.

Red blood cells sedimentation diagram was very high above the norm. In the first half-hour the red blood cells sedimented almost completely (see Table II and Fig. 2, diagram a).

TABLE II

The Comparison of the Red Blood Cells Sedimentation Diagrams

Date.	¼ hr.	1 hr.	1½ hrs.	2 hrs.	3 hrs.	4 hrs.	6 hrs.	10 hrs.	22 hrs.	
	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.	mm.	
6.8.43	157	162	164	165	166	167	168	170	173	Diagram (a)
11.8.43	109	133	144	148	152	155	157	160	162	,, (b)
17.8.43	54	95	103	108	117	122	127	132	136	,, (c)
23.8.43	3	7	14	23	39	50	61	74	99	,, (d)
30.8.43	1	3	5	6	11	14	21	34	66	,, (e)
31.8.43	...	2	4	5	8	13	17	28	57	,, (f)

After physical examination 100 c.c. of 20 per cent. glucose with ¼ mg. of strophanthin were given intravenously. This was followed by an intravenous drip of 1 pint of plasma (60 drops per minute) and an intramuscular injection of 6 c.c. hepastab.

On 7th August the patient felt better. The pulse was now 112 per minute, rhythmic and stronger. The pallor of the skin and mucous membranes, however, was even greater than on the day of admission and the number of red blood cells was found to be 820,000 per c.mm. Intravenous injection of 20 c.c. of 20 per cent. glucose with ⅓ mg. of strophanthin was recommended, followed by transfusion of 1 pint of

stored blood.   The red blood cells count rose to 1,560,000 per c.mm.
The transfusion was well tolerated.   The temperature was during the
day lower than yesterday.   Twenty-four-hour urine volume was about
1000 c.c.   The morning urine contained 0·8 per cent. albumen ; the
afternoon specimen showed a trace, later specimens were negative for
albumen.   The specific gravity was 1014-1013 and the reaction acid.
Microscopic examination of the afternoon specimen revealed per
high-power field : 4-6 white cells, 2-3 red cells, 5-10 granular casts,
brown, short, small in size and often shaped like a boomerang, a
number of epithelial cells, round and pear-shaped, yellowish in colour.
A benzidine test with the urine sediment showed a weakly positive
reaction.
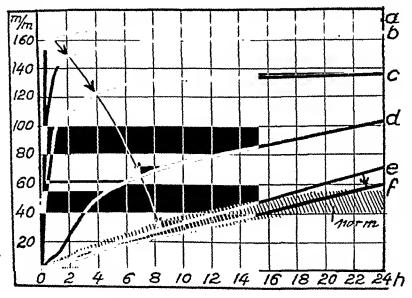
FIG. 2.

On 8th August the patient felt much better, the temperature and
pulse became more settled.   He progressed favourably from day to
day.   The strophanthin with glucose and hepastab treatment was
repeated.   Traces of hæmoglobin were present in morning specimens
of urine only ; in the afternoon urine hæmoglobin was absent.   In
order to exclude hæmoglobinuria paroxysmalis, the blood was taken
for Wassermann and Kahn tests.

On 9th August a striking improvement in the patient's general
condition was noticed.   Temperature range was now 99-99·3° F.
(37·3-37·4° C.) and the pulse 106 per minute.   The twenty-four-hour
urine was about 1½ litres.   The urine was now yellow and clear, with
an acid reaction.   Specific gravity was 1012-1004.   Albumen and
sugar were absent.   The microscopic examination of the sediment
revealed per high-power field : 4-6 white cells, 1-3 red cells, some
granular casts, brown, small, shaped like a boomerang, many oval

and round epithelial cells showing for the most part a state of fatty degeneration. The benzidine test with the urinary sediment was negative.

On 10th August improvement still continued. The patient was drinking freely and taking soft food. The temperature range was now 99-99·6° F. (37·2-37·6° C.), the pulse 106-96 per minute, rhythmic and now of good quality. Twenty-four-hour urine was about 2 litres. The urine was clear, acid and of specific gravity 1007. Tests for albumen and sugar were negative. The microscopic examination of the sediment revealed per high-power field : 2-4 white cells, 1-4 red cells, single granular brown casts and a few crystals of calcium oxalate, many round, pear-shaped and flat epithelial cells partly covered with brown grains of hæmoglobin. Fatty degeneration of the epithelial cells was still a marked feature, but the percentage of normal epithelial cells was increased.

On 11th August the general condition was good. The temperature range was 100-98·8° F. (37·8-37·1° C.) and the pulse 96 per minute, rhythmic and of good quality. He now progressed to a fairly full diet, meat being given once per day. Blood examination at this period showed the following : a degree of leucocytosis less than previous, with the red cells as after transfusion. The sedimentation diagram records the patient's favourable progress (see Table II and Fig. 2, diagram b). Urine volume over twenty-four hours was about 2 litres. The urine was yellow, clear, acid, with no albumen or sugar present in the specimen. The sediment contained very few epithelial cells, round, pear-shaped and flat, some still showing fatty degeneration, a few single white cells, no red cells, no casts. Hepastab was repeated intramuscularly as before.

On 12th August the general condition was good and the temperature normal. Skin and mucous membranes were less pale and had lost their yellowish tinge. The pulse was now 84 per minute, rhythmic, of good quality. Over the lower lobe of the right lung a few crepitations were still present. The liver was enlarged a half finger-breadth below the costal margin and was not tender on palpation. The red blood cells fragility estimation gave a normal result : hæmolysis beginning at 0·42 per cent. and being complete at 0·34 per cent. sodium chloride solution.

On 13th August the appetite was excellent and meat was given twice per day. The temperature range was now 97·6-98·8° F. (36·7-37·1° C.). Wassermann reaction was anti-complementary ; Kahn test negative.

On 16th August the skin and mucous membranes were quite pink and becoming more so each day. The liver was still enlarged a half finger-breadth below the costal margin. The spleen also was enlarged one finger-breadth below the costal margin. Both liver and spleen felt rather hard but not painful. The twenty-four-hour urine volume was about 2 litres, the urine was normal. Blood examination showed

a decrease in the number of leucocytes and an increase in the number of red cells. Reticulocytosis was a marked feature. Parasites of benign tertian malaria, both rings and amœboid forms, were discovered accidentally during inspection for reticulocytes. A detailed examination of slides which had previously been prepared on 6th, 7th and 11th August was now once again carried out but no malarial parasites were found.

The patient then informed me that six months previously he had come from the Middle East where he was resident for two years. While abroad he had felt well, and had never had at any time a malarial attack. He had taken quinine irregularly as a precautionary measure. Since arriving in Britain he had ceased to take any medicine.

On 17th August the temperature had been normal for four days. A few crepitations were still present over the lower lobe of the right lung. The sedimentation diagram revealed the great improvement in the patient's general condition (see Table II and Fig. 2, diagram c).

On 18th August malarial treatment was commenced: mepacrine 0·1 t.i.d.

On 20th August radiological examination of the chest showed an opacity of the base of the right lung, particularly marked in the cardio-diaphragmatic angle. The right diaphragm moved less than the left.

On 23rd August the sedimentation diagram was almost normal (see Table II and Fig. 2, diagram d).

On 24th August mepacrine was discontinued after seven days' administration: 0·1 t.i.d. The colour of the skin was normal. The liver reached the edge of the costal margin. The spleen was just palpable. The patient was up and walking about the wards. He felt well.

On 30th August the general condition was very good and he was allowed out to the garden. His appetite was very good and meat was included in the diet two to three times daily. His weight was now 9 stones 10 lb. (62 kg.) showing an increase of over 2 lb. (1 kg.) within the last week. No physical signs of consolidation could be discovered in the chest. The liver reached the costal margin. The spleen was not palpable. Blood examination showed red blood cell count of almost four million with the normal number of white cells. The sedimentation diagram was normal (see Table II and Fig. 2, diagram e).

On 31st August the sedimentation diagram was checked again, the result being normal (Table II and Fig. 2, diagram f).

On 3rd September the patient reached the fifth day of mepacrine, 0·1 t.i.d. The drug was well tolerated.

On 11th September the general condition was very good. The evening temperature rose from time to time to 99° F. (37·2° C.). Weight still increased. He was now 10 stones 1 lb. (64 kg.). The cytologic blood examination showed further rapid improvement. The urine was normal.

On 24th September his weight reached 10 stones 3 lb. (65 kg.). The skin and mucous membranes were normal. The liver and spleen were not enlarged. Mepacrine was given one day, 0·1 t.i.d.

On 25th September the patient was discharged to his unit, the unit medical officer being advised to dispense with fatiguing exercises and prolonged marches for a period of three months. The patient was warned never to return to any malarial locality and to avoid the use of quinine. Mepacrine 0·3 daily was prescribed on 3rd, 10th, 17th, 24th and 31st October.

On 7th February 1944 he was re-examined. The general condition was excellent. During the last few weeks he had been performing the normal soldier's duties without difficulty. His weight was now 11 stones (70 kg.), that is 5 kg. more than his weight on discharge from the hospital and 9 kg. more than his weight on the second week of the illness. The skin and mucous membranes were normal. The liver and spleen were not enlarged. No abnormality could be detected in the heart or lungs. The urine on examination gave a normal result. Blood examination showed a red cell count of 5,100,000 per c.mm. Hæmoglobin was 100 per cent.

Throughout the whole of the year 1944 the patient felt very well.

COMMENT

The case seems noteworthy on account of the following factors :—

(1) Blackwater fever is not so often encountered in a moderate climate, particularly in Britain. Modern conditions of war and travel, however, compel medical men to recognise the growing importance of tropical medicine.

(2) This attack of blackwater fever occurred in a man who had never had a single attack of malaria and who had had no quinine or any other drug for six months previous to the present illness.

(3) Blackwater fever rarely supervenes in a benign tertian infection.

(4) Physical signs during the initial period of the illness could inspire the medical officer to administer a course of sulphonamides treatment with possible bad after effects to the patient.

(5) In the case described it is difficult, if possible at all, to indicate the real " trigger that fired the gun." Possibilities are (a) excessive fatigue, (b) pneumonia, (c) a combination of both factors.

(6) This case should be considered as rather a serious one, on account of the fall in the red cells to 820,000 per c.mm. within a period of two to five days and on account of the concomitant pneumonia and heart failure.

(7) The examination of the urine immediately after admission made the diagnosis relatively easy, but if not immediately done such a diagnosis could be missed, particularly beyond the endemic area.

(8) Because of lack of brilliant cresyl blue I found that Loeffler's stain is quite satisfactory to stain reticulocytes.

(9) The sedimentation diagram is described, as far as can be ascertained, for the first time throughout such a case. On admission the diagram was very high above norm, then in twenty-five days became normal, which is an unusual course. The diagram seems to be parallel to the patient's general condition. Therefore it is suggested that the sedimentation diagram might become a good and simple test of the patient's condition in blackwater fever.

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OBITUARY

SIR HAROLD STILES

THOSE of us who knew Harold Stiles in the heyday of his surgical activities find it difficult to realise that he is now " no more." Twenty-one years ago in a manner which somehow was characteristic he finished an " out-patient day " in the Edinburgh Royal Infirmary, he bade farewell to his staff, and a few days later he was in retirement at his house in Gullane.

He had put into practice principles which he had often preached, that where surgery is concerned there is no half-way measure—that if for any reason one feels unable to give of one's best, to cease is wiser than to persevere. To those who were in touch with him at that time he said that there were days when he was conscious of being very weary ; and as he could not bear the thought of a gradual decline, he felt it preferable to lay down his task while his powers were still unspoiled. It may be that there were some who thought the decision unduly exigent, but Stiles was a man of definite opinions and when he made the sacrifice—for a sacrifice it surely was—he believed he was acting in the best interests of a profession which he regarded as something so sacred that no suspicion of inefficiency in respect of his work should attach to it.

He was strengthened in his decision by a desire to view life from an angle different from that which forty years of surgery had implied. He longed for the leisure which would permit him to follow the pursuits, and even the fancies, of a cultured mind ; to devote a portion of his days to a study of a branch of knowledge which had always held a great attraction for him—the natural sciences. He accomplished his ambition : Stiles generally did so, and in its fulfilment he found unending pleasure and unusual satisfaction.

My introduction to him was in 1908, when I applied to become his House Surgeon at the Children's Hospital. I had made an appointment to see him at his house in Great Stuart Street after his consulting hour, and as I was somewhat before my time I meandered up and down until the hour of four had struck. A cab was standing at the door—for this was before the taxi era : I concluded that it was awaiting the exit of the last patient of the day and the great man would thus be available to interview the supplicant. Presently the door opened and a slim, top-hatted, frock-coated figure dashed down the steps, entered the cab and was driven away. I had never seen Stiles, and I was under the impression that what I had witnessed was the departure of his patient ; but when I rang the bell and confronted his faithful maid of that day—Martha—she confided in me that the figure I had seen was Mr Stiles ; that he had been called away to an urgent consultation, and that I must return on the following day at the same hour. I did so, and the memory of the interview is as clear to-day as it was thirty-eight years ago. It was a shrewd and searching enquiry which went on in that book-lined room overlooking the Water of Leith. Who was I ?. What had I done ? Had I been a reputable student ? Was I interested in anatomy ?

I had a feeling that I didn't make a good impression, but I was reinforced by a much too flattering recommendation from Mr J. W. Dowden, and to

HAROLD JALLAND STILES

this day I believe that it was this which turned the scales in my favour. His shade will forgive me if I say that in these days he was apt to be a little terrifying to the incompetent.

Well do I recall the occasion when, as his House Surgeon, I had persuaded him to operate on a baby for a hernia which wasn't there. It happened to be on the opposite side ! In his characteristic high-pitched voice, with the slight hesitation of speech which was both arresting and attractive, he said, " I always overlook one mistake, but a second of the same kind I cannot tolerate." As a comment it was perfectly fair, and if it was disconcerting it certainly elicited efficiency.

These things marked the beginning of a long friendship : an association which for me took the character of hero-worship, of an admiration which grew as the years went by. Our last meeting was in the beginning of April of this year, ten days before his death. The years—for he was in his eighty-third spring—had taken a toll, as indeed they must do. There was the mellowing which age so often brings, but the intelligence seemed to be as acute as on the day when first I met him thirty-eight years before. Now it was botany and geology which claimed his attention, though the interest in surgery remained. At least I underwent a close cross-examination on events present and to come, and it was remarkable to listen to his shrewd comments and searching criticism. He was full of glad expectations about his immediate future, and the evening of his day was tinted by the colours of happiness and content.

What I write is a personal appreciation, and I do not know that I need recount the features of his interesting and distinguished career. Abler pens than mine have fulfilled the task, but perhaps I may be permitted to indicate certain of the stages by which he rose to fame and honour. Stiles represented the third generation in a line of East Lincolnshire general practitioners. It was intended that Harold and his brother should follow the family tradition, and with this object in view and in the spirit of the day he served what may be described as a period of apprenticeship in his father's practice. It was at this time that his remarkable interest in anatomy became apparent. By his own account he had memorised a large part of *Heath* before he began the study of medicine, and certain it is that an intimacy with anatomical detail was one of the most impressive features in his operative technique. He was one of the many who succumbed to the charms of Scotland's capital city. In his *Reminiscences*, published in 1920, he recalls that on his first evening in Edinburgh, in May 1880, he climbed the Calton Hill, and so struck was he by the beauty of the scene which lay around him that : " I vowed that . . . I would endeavour to make my home in Edinburgh and that I would not leave it unless I was starved out." Fortunately for the Edinburgh Medical School he adhered to this early resolve ; but it was not in keeping with his father's wishes, and when he graduated in 1885 with first-class honours and the award of the Ettles Scholarship, the parental injunction was " well done, but now you must fish for yourself." A year was spent in residencies in the Edinburgh Royal Infirmary : one medical, with Sir Thomas Grainger Stewart, the other surgical, with Professor John Chiene. Then began the " fishing " which his father had forecast and, to continue the simile, three " landings " afforded him some degree of early security—a junior assistantship in the Department of Surgery ; a post as demonstrator under Sir William Turner ; and a coach class which he conducted in conjunction with Alexis Thomson. But the beginning had its difficulties, and sometimes

he recalled that when he arrived in Edinburgh to take up these various appointments, the exchequer was so depleted that it was an understanding landlady. in Forrest Road, with whom he lodged, who advanced the means whereby the " cabby's " claim was met. *Jucundi acti labores!*

The opportunities afforded in the Surgery Department had an important effect upon his career. Chiene, with creditable foresight, had established a laboratory where bacteriology and pathology in relation to surgery were pursued. Stiles was particularly attracted by the pathological work; he introduced the NAPLES or paraffin immersion method by which tissues were prepared for section and microscopic examination; and it was from these beginnings that he carried out his research on lymphatic dissemination in carcinoma of the breast, which was awarded in 1896 the Walker Prize of the College of Surgeons of England, and upon which the modern operation for carcinoma of the mamma is based.

I wonder how many are aware of the fact that Stiles deserves the credit of having introduced the aseptic technique into Edinburgh hospitals? It happened in this wise. He spent the summer and autumn of 1893 in Professor Kocher's Clinic at Berne, where he witnessed the use of high-pressure steam as a means of sterilisation, and a surgical procedure which was based upon aseptic methods. To Stiles—a product of the Listerian School—he had been " Spray Clerk " in Chiene's clinic—the Swiss technique presented a striking contrast, but he was soon convinced of its outstanding advantages, and when he returned to Edinburgh he urged the adoption of the method.

His advocacy bore fruit. When he was appointed surgeon to the Children's Hospital in 1898 he persuaded the Directors to instal a steam steriliser on the Swiss model, and so great were the advantages of the method that, a few years later, the Royal Infirmary adopted a similar arrangement.

His appointment to the honorary staff of the Royal Infirmary came in 1895 when he was elected an assistant surgeon; but his term of office was short, for three years later, when the post of Surgeon to the Children's Hospital became vacant on the retirement of Dr Joseph Bell, Stiles was selected to succeed him. The appointment necessitated his retirement from the Royal Infirmary, and doubtless there were many who at the time questioned the wisdom of the choice. But Stiles acted on his own judgment—he rarely did otherwise—and in this instance events showed that he had made no mistake. Under the influence of his enthusiasm the surgical section of the Children's Hospital became a centre of activity which attracted widespread interest; and presently an adult hospital association was re-established, when he was appointed Surgeon to the Chalmers Hospital.

His reputation was now fully established; he enjoyed a large and increasing practice as a consultant, yet he found time and opportunity to develop his great ability as a teacher, and to pursue his interests in the scientific aspects of his surgical work. An illustration of this is found in the contribution which he made to our knowledge of surgical tuberculosis.

Clinical observation led him to the conclusion that the bovine bacillus played an important part in originating the disease in man, and particularly during childhood. Such views were in opposition to those advanced by Koch, but Stiles was convinced of the accuracy of his own deductions; and the various investigations on bone, joint, and gland disease which he initiated established the truth of his contention. It was a far-reaching contribution to a problem of considerable social and economic significance.

During the war of 1914-18 he acted as a consultant in the Army Medical Service with the rank of Colonel. His interests centred on orthopædics, and in conjunction with the late Sir Robert Jones he was responsible for the organisation which was established at Bangour, and which rendered such outstanding service in the immediate treatment and the rehabilitation of the wounded.

He was knighted in 1918, and in 1919 in recognition of his war services he was created a K.B.E.

On the retiral of Professor Caird in 1919 Stiles succeeded him in the Chair of Clinical Surgery. The appointment gave general satisfaction, and Stiles welcomed it because it offered abundant opportunity for an activity which he loved—clinical teaching—moreover there was the satisfaction of returning to the hospital in which his surgical career had begun. His tenure of office was brief, however. He believed in the principle of early retirement, particularly where surgery is concerned, and in September 1925 he resigned from the Chair and moved to his country home at Gullane. It was a change of interest rather than complete retirement. Geology became his delight, and he studied it with the intensity which he had bestowed upon surgery. Field work at home and abroad afforded him particular pleasure. As his physical strength declined and journeyings became difficult, he took up botany as a pursuit which he could enjoy within the surroundings of his home. He found the keenest pleasure in the subject, and until within a few days of his death he was busy with the task of identifying and sketching the flora of East Lothian.

As we say *Vale*, we salute the memory of one who brought credit and distinction to the Edinburgh Medical School and to British Surgery.

J. F.

DR PETER McBRIDE (1854-1946)

THE recent death of Dr Peter McBride at the age of ninety-two years has severed the last remaining living link with the early days of laryngology in Edinburgh. Born in Hamburg, Peter McBride was educated at Clifton College and Edinburgh University. After qualifying M.B. in 1876, he served as house physician in the Royal Infirmary, and became M.D. in 1881. He was elected a Fellow of the Royal College of Physicians in 1880. Unlike otology, which was a surgical specialty from the first, laryngology was a child of medicine and the laryngologist was a physician.

McBride amplified his studies in Vienna, then the medical post-graduate teaching centre of the world, and on his return to Edinburgh he was appointed Surgeon to the Eye, Ear and Throat Infirmary in Cambridge Street and Lecturer on Diseases of the Ear, Nose and Throat in the Extra-Mural School of the Royal Colleges. Otology and laryngology were studied and practised as separate subjects in London, Glasgow and elsewhere, but in Edinburgh they were united from the first. In 1883 a department consisting of one small room in which patients were seen twice a week was allotted to the specialty in the Royal Infirmary, and in 1897 the University established a lectureship on Diseases of the Ear, Nose and Throat. Dr McBride was the first to hold each of those appointments, and it was largely owing to his hard work and initiative that a fully equipped department was established before his retirement in 1903. His writing was clear and concise and it is not surprising

that his text-book, *Diseases of the Throat, Nose and Ear*, originally published in 1891, retained its popularity through three editions. In the preface to that work, one may find a statement which reveals the logical mind of the writer : " All drawings of instruments have been omitted. . . . They are unnecessary for the simple reason that the practitioner must possess the means of operating before he proceeds to operate."

Dr McBride's ability won for him many honours : in 1883 he became a Fellow of the Royal Society of Edinburgh, he was President of the Laryngological Society of London, of the Otological Section of the Royal Society of Medicine and of the Section of Otology and Laryngology at the British Medical Association Meetings ; he was also elected an Honorary Member of the Scottish Otological and Laryngological Society. In 1913 he delivered the Semon Lecture at the University of London. On retiring from practice in 1910 he went to live in Yorkshire, at first at Harrogate and latterly at York. There, so long as health and energy permitted, he indulged his favourite sport of hunting. Throughout his life he took a keen interest in all sports and games. His years of retirement were also employed in writing interesting contributions to philosophy and psychology. Perhaps the most popular of those works are his essay entitled *Psychoanalysis Analysed* (1924) and his later *Philosophy of Sport* (1932).

Peter McBride was a charming companion, and it was a great pleasure for old friends to renew acquaintance with him during his frequent visits to Edinburgh after his retirement. It was characteristic of him that during the war of 1914-18 he returned to voluntary work as laryngologist at the 2nd Scottish General Hospital under Dr Logan Turner, who had formerly been his assistant. Endowed with a rich fund of humour, he was an excellent raconteur. At the close of his long and useful life we honour the memory of this doughty pioneer of laryngology.

D. G.

NEW EDITIONS

Preventive Medicine. By MARK F. BOYD. Seventh Edition. Pp. 588, with 168 illustrations. Published by W. B. Saunders Company Ltd., Philadelphia. 1945. Price 27s. 6d.

This book presents the minimum knowledge of the subject which a student of medicine should be expected to possess.

Of a total of 588 pages, no less than 340 are devoted to diseases of microbal origin ; some 74 to nutrition ; 21 to occupational health ; 9 to the puerperal state ; 10 to heredity and disease ; 47 to the hygiene of infancy and childhood, air, heating, ventilation and personal hygiene ; 34 to demography and 11 to public health organisation and administration.

It is the seventh edition of a book that has long claimed its place in medical literature. It is, of course, an American textbook, and American problems and conditions therefore receive special attention.

It is well worthy of study by British hygienists, however, for it is very well written, well illustrated and well produced. It is to be noted, however, that developments in the field of social medicine in this country have robbed most of the existing textbooks on preventive medicine of much of their former usefulness.

Textbook of Public Health. By W. M. FRAZER, O.B.E., M.D., CH.B., M.SC., D.P.H., and C. O. STALLYBRASS, M.D., CH.B., D.P.H., M.R.C.S., L.R.C.P. Eleventh Edition. Pp. 571, with 78 illustrations. Published by E. & S. Livingstone Ltd., Edinburgh. 1946. Price 25s. (Formerly Hope and Stallybrass.)

This is the eleventh edition, revised and enlarged, of a book that on its merits as long since claimed its place among the best British textbooks on the subject.

In this edition, the chapter on "The Medical Aspects of Civil Defence" is omitted—a somewhat intriguing indication that the preceding edition and this one bridged the war years.

This is an excellent manual for those proceeding to the Diploma in Public Health governed by the new rules of the G.M.C.

In the field of public health. At the moment this field is changing exceedingly rapidly, so rapidly that no textbook could hope to satisfy the needs of the several teachers who are giving definition to social medicine. But this book is as good as any and better than most, for it does cover the ground both of the Certificate and the Diploma.

Disorders of the Blood. By Sir L. E. H. WHITBY, C.V.O., M.C., M.A., M.D., F.R.C.P., D.P.H., and C. J. C. BRITTON, M.D., D.P.H. Fifth Edition. Pp. xii+665, with 71 figures and 15 plates. London : J. & A. Churchill. 1946. Price 30s. net.

This outstanding work has become the recognised standard in the subject. For this edition extensive revision has been carried out, the text has been increased by sixty-two pages and four new coloured plates of bone marrow have been introduced. Additional material has been included in the sections dealing with the origin and development of the blood cells, the hæmolytic anæmias, the anæmias of infancy and childhood, hæmagglutination and blood transfusion and technique. *Continued*

BOOKS RECEIVED

ABBIE, A. A., M.D., B.S., D.SC., PH.D.   The Principles of Anatomy.   Second
   Edition   .   .   .   .   .   (*Angus & Robertson Ltd., Sydney*)   12s. 6d. net.
ANDERSON, W. A. D., M.A., M.D., F.A.C.P.   Synopsis of Pathology.
   (*Henry Kimpton, London*)   32s. 6d. net.
BAETJER, ANNA M., SC.D.   Women in Industry : Their Health and Efficiency.
   (*W. B. Saunders Co., London and Philadelphia*)   20s. net.
BAILEY, HAMILTON, F.R.C.S., F.I.C.S.   Demonstrations of Physical Signs in
   Clinical Surgery.   Tenth Edition, Revised.
   (*John Wright & Sons Ltd., Bristol*)   30s. net.
BROWNE, FRANCIS J., M.D., D.SC., F.R.C.S., F.R.C.O.G.   Antenatal nnd Postnatal
   Care.   Sixth Edition   .   .   .   (*J. & A. Churchill Ltd., London*)   25s. net.
CRAIG, W. S., B.SC., M.D., F.R.C.P.E., F.R.S.E.   Child nnd Adolescent Life in
   Health nnd Disease   .   .   (*E. & S. Livingstone Ltd., Edinburgh*)   25s. net.
CROMWELL, GERTRUDE E., R.N.. M.S.   The Health of the School Child.
   (*W. B. Saunders Co., London and Philadelphia*)   12s. 6d. net.
CURTIS, ARTHUR HALE.   A Textbook of Gynecology.   Fifth Edition with
   455 Illustrations   .   .   (*W. B. Saunders Co., London and Philadelphia*)   40s. net.
DOBSON, JESSIE, B.A., M.SC.   Anatomical Eponyms.
   (*Baillière, Tindall & Cox, London*)   30s. net.
ENGLISH, Sir CRISP, K.C.M.G., F.R.C.S.   Patients and Appendicitis.
   (*J. & A. Churchill Ltd., London*)   10s. 6d. net.
Essays by ALBERT FISCHER.   Biology of Tissue Cells.
   (*Cambridge University Press, London*)   31s. 6d. net.
FARRELL, JOHN T., Jr., M.D.   Roentgen Diagnosis of Diseases of the Gastro-
   intestinal Tract   .   .   .   (*Charles C. Thomas, Illinois, U.S.A.*)   30s. net.
GILMOUR, W. SANTON, M.B.   Tuberculosis in the West Indies.
   (*National Association for the Prevention of Tuberculosis, London*)   —
HARROW, BENJAMIN, PH.D.   Textbook of Biochemistry.   Fourth Edition,
   Illustrated   .   .   (*W. B. Saunders Co., London and Philadelphia*)   22s. net.
HARVEY, WM. CLUNIE, M.D., D.P.H., M.R.SAN.I., and HILL, HARRY, F.R.SAN.I.,
   A.M.I.S.E., F.S.I.A.   Milk : Production and Control.   Second Edition.
   (*H. K. Lewis & Co. Ltd., London*)   37s. 6d. net.
KATZ, LOUIS N., A.B., M.A., M.D., F.A.C.P.   Exercises in Electrocardiographic
   Interpretation.   Second Edition   .   .   (*Henry Kimpton, London*)   30s. net.
KATZ, LOUIS N., A.B., M.A., M.D., F.A.C.P.   Electrocardiography.   Second
   Edition   .   .   .   .   .   (*Henry Kimpton, London*)   60s. net.
KEY, JOHN ALBERT, B.S., M.D., and H. EARLE CONWELL, M.D., F.A.C.S.
   The Management of Fractures, Dislocations and Sprains.   Fourth Edition.
   (*Henry Kimpton, London*)   63s. net.
KLYNE, WILLIAM, M.A., B.SC.   Practical Chemistry.
   (*E. & S. Livingstone Ltd., Edinburgh*)   20s. net.
McCLUNG, L. S.   General Bacteriology Laboratory Manual.
   (*W. B. Saunders Co., London and Philadelphia*)   6s. 6d. net.
MACKENNA, ROBERT M. B., M.A., M.D., B.CH., F.R.C.P.   Aids to Dermatology.
   Third Edition   .   .   .   (*Baillière, Tindall & Cox, London*)   6s. net.
MAIN, ROLLAND J., PH.D.   Synopsis of Physiology (*Henry Kimpton, London*)   18s. net.
OSMOND, T. E., B.A., M.B., M.R.C.S., L.R.C.P.   Aids to the Diagnosis and Treat-
   ment of Venereal Diseases   .   .   (*Baillière, Tindall & Cox, London*)   5s. net.
PINEY, A., M.D., M.R.C.P., and J. L. HAMILTON-PATERSON, M.D., M.R.C.S.
   Sternal Puncture.   Third Edition.
   (*William Heinemann (Medical Books) Ltd., London*)   —
RICHARDS, ROBERT L., M.D.   The Peripheral Circulation in Health and
   Disease   .   .   .   .   (*E. & S. Livingstone Ltd., Edinburgh*)   21s. net.
ROBERTS, LLYWELYN, M.D., M.R.C.P., D.P.H.   Aids to Public Health.   Fifth
   Edition   .   .   .   .   (*Baillière, Tindall & Cox, London*)   6s. net.
SCHLOSSER, RUDOPLH O., D.D.S., F.A.C.D.   Complete Denture Prosthesis.
   Second Edition with 288 Illustrations.
   (*W. B. Saunders Co., London and Philadelphia*)   27s. 6d. net.
SUTTON, G. E. FREDERICK, M.C., M.D., M.R.C.P.   Aids to Medical Diagnosis.
   Sixth Edition.   .   .   .   (*Baillière, Tindall & Cox, London*)   6s. net.
TRAQUAIR, H. M., M.D., F.R.C.S.ED.   An Introduction to Clinical Perimetry.
   Fifth Edition   .   .   .   .   .   (*Henry Kimpton, London*)   36s. net.
TRUETA, J., M.D., D.SC.   The Principles and Practice of War Surgery.   Third
   Edition   .   .   (*William Heinemann (Medical Books) Ltd., London*)   42s. net.

Edinburgh Medical Journal

SARCOIDOSIS—A MANIFESTATION OF TUBERCULOSIS

By CHARLES CAMERON, M.A., M.D., F.R.F.P.S., D.P.H.
Professor of Tuberculosis, University of Edinburgh,
and E. K. DAWSON, M.A., M.D.*
*From East Fortune Sanatorium and the Research Laboratory
of the Royal College of Physicians, Edinburgh*

IN a previous paper (1942) we discussed the ætiology of sarcoidosis, and stated that while there was much against the idea of a tuberculous basis, there were sufficient resemblances, clinical, radiological, and histological, to suggest a probable causal relationship. Since then the conviction has been growing that sarcoidosis is an atypical form of tuberculosis, and we now record, and use as the basis of our discussion, a case of pulmonary tuberculosis with pathological changes in other tissues which conformed with the accepted clinical and histological features of sarcoidosis. This patient presented features of unusual interest, and we make no apology for recording the history and clinical condition in some detail.

HISTORY

A. B., aged fourteen and a half years, was admitted to East Fortune Sanatorium on 16th August 1941. Her history was the following :—

She was a healthy, normal baby, and she was in good health until the age of five years when she developed pain in the calves of her legs and was admitted to the Royal Hospital for Sick Children, Edinburgh, as a suspected case of rheumatic fever. There were no joint swellings. She was discharged after a period of six months' treatment and attended the rheumatism clinic of the hospital as an out-patient. At about the age of six, *i.e.* a year after the onset of her symptoms, swelling of both knees and ankles appeared. The onset was sudden and painless and was discovered by her mother as she was bathing her. She was re-admitted to the hospital and kept for a further period of six months. The joints remained free from pain and their condition was unchanged at the time of her discharge. She had two subsequent periods of treatment in Chalmers Hospital, Edinburgh, and the swellings remained confined to the ankles and knees. They caused no pain and they were unaffected by treatment. At about the age of eight cough appeared and it was about this time that the mother noticed swelling of her finger tips and slight lividity of her face. On account of the cough she was taken to the Royal Victoria Dispensary where she was kept under observation for three months. Later, a diagnosis of lung tuberculosis was made in the Sick Children's

* Grantee, Edinburgh and South-East Scotland Cancer Control Organisation.

Hospital. During the following year, when she was about nine, a livid mark like a bruise, appeared on the front of the left leg below the knee and she had a succession of these marks during the following few months. The marks were like bruises and were sparsely disposed over the front of both lower legs and thighs. As they faded they were replaced by others. They were nodular and they did not ulcerate. There was no associated disturbance of health and the cough and joint swellings persisted.

On account of her constant illness she was educated at home by a visiting teacher and in September 1939 she was evacuated with other crippled children to Earlston, in Berwickshire. In November 1939 she was admitted to the Princess Margaret Rose Hospital for treatment of her swollen but painless joints and there, in January 1940, she had an attack of " pneumonia " of her right lung. She recovered after an acute illness which lasted a week and was followed by cough and weakness which were troublesome during the following two months. It was in that hospital that the mother was told for the first time that the child had heart disease. She was discharged in August 1940 and returned to Earlston. The joints remained swollen and she continued to cough. In September 1940 she had a recurrence of fever and pain in the right side of her chest and was admitted to the County Hospital, Gordon, as a case of lung tuberculosis. She remained there until August 1941 when she was transferred to East Fortune Sanatorium.

CONDITION AT TIME OF ADMISSION
AND SUBSEQUENT HISTORY

She was a thin little girl, poorly developed for her years, but alert and intelligent. Her face and lips were very livid and her finger-tips were cyanosed and bulbous. She had a hydrarthrosis of each knee, gross in the left, and there was synovial swelling of both ankle joints. All of the joints were painless and moved freely. There was a loud heart murmur which was considered to be due to mitral stenosis, although the other signs suggested congenital heart disease. She had a cough and brought up a scanty mucopurulent spit, and she had diffuse abnormal signs in both lungs. These signs were very suggestive of bilateral upper lobe tuberculosis, but they extended to the bases and an open mind was kept on their relationship to the heart disease. Her tonsils had been removed and her fauces were healthy, but she had many carious teeth. The Mantoux (1 : 1000) reaction was +++. The blood Wassermann, Kahn, and Flocculation tests were negative.

X-ray examination of her chest showed gross dilatation of the pulmonary artery, a huge mass of glands in the right lung root, and what looked like a chronic fibrotic tuberculous lesion of the right upper lung lobe. Films of the joints showed a bilateral knee effusion. Otherwise they suggested a low-grade infective arthritis of all four affected joints.

Fifteen sputum film examinations failed to reveal the presence of tubercle bacilli, but a culture made on L.J. medium yielded a profuse pigmented growth of tubercle bacilli. Typing was not performed and the organism was presumed to be of the human type. The diagnosis of lung tuberculosis was thus confirmed and the somewhat anomalous

appearance of some of the lung X-ray shadowing was considered to be due to a combination of congestion and tuberculosis. The relationship of the abnormal joints to the heart condition was not clear, and three separate pathological conditions seemed to be present.

Her temperature was slightly but irregularly raised, her pulse-rate ran from 100 to 120, and the blood pressure was 104/80. The blood sedimentation rate was not investigated at that time. Later it ranged between 30 and 40 mm. (Westergren).

At the beginning of November 1941 she complained of inability to see and she was found to have bilateral iridocyclitis. Dr E. H. Cameron saw her on 9th November and confirmed the diagnosis. He found posterior synechiæ in both eyes, a deposit in the left iris, deposits behind the left cornea, and cloudiness of each vitreous. The condition in his opinion was of tuberculous origin and he gave a bad prognosis.

The urine at the time of her admission contained albumen in fairly large quantity—a dense coagulate on boiling—and that persisted. The sediment contained a few granular tube casts. She had no nephritic symptoms and more complete investigation was not made. On 4th December 1941 she had hæmaturia, the urine being bright red with blood. Her lower gums around the incisor teeth were livid and tender, and on 7th December the carious first lower incisors were extracted. Blood cultures were sterile. The urine was now found to contain a little pus which was cultured for tubercle bacilli with negative results.

Blood examination on 12th December showed a red cell count of 5,230,000 and a white cell count of 9400. The red cells were normal in form and size. A hæmoglobin estimation was not made. The differential white cell count was:

	Per Cent.
Polymorphs	70
Large lymphocytes	7
Small lymphocytes	15
Mononuclears	4
Eosinophils	3
Mast Cells	1

During the early months of 1942 her condition improved. The iridocyclitis subsided and the vision became better. Cough and spit disappeared and the heart murmur was no longer audible. She continued to have slight, irregular, varying fever.

In June her liver became palpable. Some more carious teeth were extracted, a few at a time. The state of the urine and of the joints remained unchanged.

Her condition remained much the same until 22nd March 1943, when she had a sudden attack of right loin pain associated with fever and the passage of pus in the urine. The condition was clinically pyelitis. T.B. were not found in pus smears. The attack subsided and the temperature settled a week later to its old, slightly febrile, level. Albuminuria persisted and a little pus remained in the urine.

On 27th April 1943 there was noticed during routine examination a blotchy, slightly scaly, livid, maculo-erythematous rash on both legs below the knees. Some of the blotches were indurated marginally and soft in the centre. The rash disappeared in ten days but returned two months later. It was then generalized, dense on the face and limbs, and sparse on the trunk. Dr Robert Aitken saw her on 29th June 1943. He made a tentative diagnosis of pityriasis rubra but pointed out that the rash was not typical of that condition. The rash came and went, clearing sometimes for a week or two and returning with increasing intensity. The skin of the limbs, forehead, and cheeks in time became permanently pigmented and infiltrated.

On 1st February 1944, again during routine examination, clusters of big, soft, painless, mobile glands were discovered ·in each axilla and groin. Albuminuria (Esbach 5 parts) and slight fever persisted and the lung X-ray appearances were unchanged. Big masses of glands were still seen in the right lung root, and shadowing of the right upper lobe now looked like that of healing fibrotic tuberculosis. Atypical shadowing in other areas of the lungs began to look very like sarcoidosis, and on 4th February a gland was excised from the right axilla and sent to Professor Murray Drennan for histological examination. On 14th February Professor Drennan reported that the sections showed diffuse permeation by columns of large, clear, endothelioid cells which lay throughout the sinus system and largely replaced the lymph follicles. Giant cells were present but there was no caseation or fibrosis, and tubercle bacilli were not found. The picture, in his opinion, " resembled the sarcoid appearance although it might be an endothelioid response to tuberculous toxin." The inoculation of a guinea-pig with a gland was recommended and another gland was removed on 25th February and sent for that purpose. Culture of the emulsified gland˔ was negative for tubercle bacilli, and the inoculated guinea-pig failed to develop tuberculosis.

Although she had little in the way of symptoms—nothing more than a slight dry cough—extensive abnormal signs persisted in the lungs. These were considered to be suggestive of fibrosing tuberculosis of the right upper lobe and of the lower two-thirds of the left lung. The X-ray appearance will be discussed more fully later. The heart murmur remained absent, she had no heart symptoms, and the lividity of admission was no longer present. The finger clubbing was unchanged.

During July 1944 a deep infiltration of the soft tissues of the right. loin was noticed. Big soft discrete glands were palpable and visible in the axillæ and groins, in the left deep iliac area, and in the right epitrochlear region. A complete blood examination on 24th August gave the following result :—

				White Cells	Per Cent.
R.B.C. .	.	. .	6,150,000	Polymorphs . . .	. 75
W.B.C..	.	.	8,000	Lymphocytes . . .	. 19
Hb	.	.	108	Monocytes . . .	. 2
C.I.	.	.	0·9	Eosinophils . . .	. 3
				Basophils . . .	. 1

On 3rd November 1944 gastric lavage produced a few small blobs of mucoid sputum. T.B. were not found in smears but culture yielded a fairly profuse growth of tubercle bacilli which, by animal inoculation, were found to be the human type of normal virulence. Meantime, another axillary gland was excised and sent to the Royal College of Physicians' Laboratory. Colonel Harvey reported that the appearances were more suggestive of sarcoidosis than of any other condition.

On 7th December 1941, during the examination of smears from urinary sediment, one of us (C. C.) had found a cluster of acid-fast bacilli which, morphologically, were tubercle bacilli. Culture from the same sediment on L.J. medium was, however, negative, and another culture made on 3rd November 1944 was also negative. Slight symptomless pyuria continued. The blood urea on 5th February 1945 was found to be 56 mgm. per cent., and in subsequent estimations it varied between 30 and 50 mgm. per cent. A urea clearance test performed on 20th February gave a clearance figure of 11 c.c. per minute with a final estimated result of 21 per cent. of normal. On this day the albuminuria had increased to a figure of 8½ Esbach. The total serum protein was 5·72 gm. per cent., the albumen being 2·29 and the globulin 3·43. The blood cholesterol was 235 mgm. per cent. The daily output of urine was about 60 ozs. and during repeated examinations of the urinary sediment pus cells in moderate numbers were found. A very occasional red cell and epithelial cell were seen and a still more occasional hyaline or granular cast. The blood pressure was around 110/76 and there was no œdema.

Dr Aitken saw her again on 27th December 1944. He classed the rash as a dermatitis of internal origin and he had no doubt that it was part of the sarcoid condition. He pointed out that it had practically missed the trunk. There was livid, and in places brown, staining of the face, limbs, and buttocks, and the involved skin was filtrated and thickened. On 10th January 1945 a piece of skin from area of infiltration in the right thigh was excised and sent to the Royal College of Physicians' Laboratory. It was found to show typical histological sarcoid changes.

As a clinical problem, there were thus four distinct conditions— disease of the heart, arthritis of the knee and ankle joints, tuberculosis of the lungs, and the sarcoid manifestations. To this may be added her failure to develop. At the age of eighteen and a half, she measured 4 ft. 8 in., weighed 4 stones 7 lbs., and showed no secondary sexual changes.

Dr Lewis Thatcher very kindly gave us information about her early illness in the Sick Children's Hospital. Unfortunately her full case notes were not available, but Dr Thatcher was able to state that she had an intermittent and fleeting polyarthritis with occasional slight enlargement of the spleen. There was nothing to suggest carditis or congenital heart disease. The probability of Still's disease was

considered and discarded as the condition was more of a painless hydrops and there was never any evidence of periarthritis. The mediastinal shadow on the X-ray film was somewhat increased but there was no real evidence of active tuberculosis.

On 27th November 1944 Dr Rae Gilchrist kindly saw her in the Royal Infirmary. Electrocardiographic examination showed a well-marked right axis deviation with a sinus tachycardia, the rate being 100. After a careful discussion of the clinical and radiographical findings, Dr Gilchrist stated his opinion that the most likely diagnosis was a patent interauricular septum. That congenital condition could have no possible relationship with the subsequent joint affection.

The nature of the arthritis is doubtful. Dr Saffley interpreted the X-ray appearances of the knees as being those of a subacute arthritis, their essential elements being synovial thickening and generalised decalcification. The ankle joint films also showed generalised decalcification, and he called attention to a prominence of the trabeculæ in the lines of weight-bearing which, in his opinion, was more typical of a general constitutional disturbance than of a local infection ; but the clinical state of both sets of joints was the same and swelling of each had developed simultaneously.

It is difficult to place this joint condition in a definite category. Dr Thatcher has pointed out that the condition was originally a hydrops ; latterly, synovial thickening was a prominent feature. The later development of glandular enlargements might suggest Still's disease, but the joints have remained mobile and painless and the glands have been found to show typical sarcoid changes. The blood sedimentation rate has varied consistently between 30 and 40, and the swelling of the knees certainly lessened after the removal of the last of her carious teeth in August 1944. Permission to procure a biopsy specimen from a joint was not granted. We return to this question later.

It is equally difficult to associate the urinary and allied findings with any of the other conditions and, for that matter, to fit them into a definite pathological picture. They are those of a kidney lesion of the nephrotic type, but they conformed definitely neither to the lipoid nor amyloid varieties. Latterly the blood urea rose, the urinary output fell, and she developed œdema of her legs and ankles. That, in all probability, was of cardiac origin. The blood pressure remained low—108/66.

The lung tuberculosis with its gross hilar gland enlargement was like a primary infection which had proceeded to ulcerative disease, but its course was characterized by extreme torpidity. The disease was in the right upper lobe, but X-ray films showed other changes which it was extremely difficult to interpret and before the appearance of the glandular enlargements their resemblance to sarcoidosis had been noted. Whether there is any X-ray picture which is diagnostic of lung sarcoidosis is a moot point, but the combination of striation and ill-defined, fine nodular shadows, with gross hilar glandular

enlargement, forms the basis of the sarcoid change. Lung tuberculosis was diagnosed when she was nine years of age, but there is no record of its having been proved at that time. The gross sarcoid developments took place after her admission to the sanatorium and it is here that the main interest of the case lies; for this is a case of lung tuberculosis (proved by repeated cultivation of tubercle bacilli from sputum) characterised by a regressive tendency, which later developed iridocyclitis, enlargements of glands, and skin changes, the latter two of which were proved histologically to be of a sarcoid nature.

LATER HISTORY

In January 1946 she developed influenza and became extremely ill with symptoms and signs of a bronchopneumonic character. She survived the acute stage, and when one of us (C. C.) gave up charge of the Sanatorium at the end of January we lost clinical contact with her. She was then dyspnœic and had a troublesome cough. She never recovered from this illness and for the later notes of her condition we are indebted to Dr W. A. Murray.

From the beginning of this terminal illness early in January she was drowsy and thirsty, and on 18th January the blood urea was found to be 100 mgm. per cent. The urinary output fell to 30-35 ozs. daily, but much fluid was being lost by sweating and, towards the end, by diarrhœa. On 24th January the blood urea was 88 mgm. per cent., and on 22nd February it was 125 mgm. per cent. On that day an estimation of the plasma proteins gave a total figure of 7.75 gm. per cent., with albumen 1.3 gm. and globulin 6.45 per cent. Nausea and thirst were then constant and she had troublesome watery diarrhœa. She became progressively more breathless, had a troublesome cough, and brought up with difficulty about ½ oz. daily of thick mucopurulent sputum in which tubercle bacilli were now found on ordinary smear examination (on 10th February). The lung signs were of a diffuse bronchitic and bronchopneumonic character and the heart was evidently failing. She was taken home by her parents on 9th March and she died two days later.

The last X-ray examination was made on 11th January while she was in the acute phase of her illness. Calcification of the glands in the right lung root was well advanced and the hilar mass was much smaller and comparatively well-defined. There was the same gross dilatation of the pulmonary conus and the same restricted fibrotic tuberculous disease of the right upper lobe containing multiple small cavities and numerous areas of calcification. There was an area of bronchopneumonic shadowing at the left base and fairly diffuse shadowing throughout the remainder of the left lung and over a wide central area of the right, difficult to interpret, but probably of a congestive nature. Death was not primarily from tuberculosis. It was essentially a cardiac death. How much was contributed by the kidney lesion is doubtful. There was at no time hypertension.

THE PATHOLOGY OF SARCOIDOSIS

Many cases in the literature are accompanied by illustrations of the pathological changes in sarcoid lesions and our previous study showed these changes in various tissues.   Further examples are given in the accompanying plates.   The present case shows no unusual histological features, though giant cells of varying size were fairly numerous in some areas of the lymphoid tissue (Figs. 4, 6 and 7).   In general, the folliculoid formations tend to remain more even in size and more discrete than in active tuberculosis (Figs. 3, 11), but a strand arrangement of the endothelioid cells or a granulation tissue of more diffuse character with irregularly scattered giant cells (Figs. 4, 6) may be formed.   The cutaneous lesion here showed the characteristic structure, with stranded architecture, few giant cells and little lymphocytic cell reaction (Figs. 8, 9).   Though, clinically, a distinction is made between Boeck's cutaneous sarcoid and the Darier-Roussy subcutaneous variety, a lesion of long duration may show continuous extension of the proliferating tissue from the subepidermal zone (Fig. 8) down to and into the subcutaneous fat (Fig. 9).

Most recorded histological examinations have been made in cases of some duration, when the characteristic structure is evident and also, as Kyrle (1921) has shown, when it is too late to recover the bacillus. In a case of acute, generalised, cutaneous involvement, with successive biopsies, Kyrle found the bacillus and a mainly lymphocytic cell reaction in foci under ten days old ; by the thirty-sixth day there was destruction and disappearance of the organism and the formation of the typical Boeck's miliary sarcoid.   An intermediate picture, at twenty-one days, showed both lymphocytic and endothelioid cells, with few bacilli.   In this, therefore, as in so many other lesions, the histology varies with the age of the condition ; later stages show fibrosis and progressive hyalinisation and, in some tissues, calcification. In the lymph node tissue from this patient, many of the giant cells showed curious " inclusions " of an undetermined nature (Figs. 5, 7) ; these may be associated with the rapid destruction of the bacilli.

The widespread distribution of sarcoid lesions in the various organs and tissues suggests a mainly hæmatogenous dissemination, represented histologically by the different stages of follicle formation in the same and in different tissues, apparently associated with repeated, small, blood-borne seedings.   This widespread involvement is well shown in the cutaneous distribution in our patient (Figs. 1, 2).

It is difficult to estimate how frequently sarcoidosis occurs. It is probable, as the literature indicates, that many cases are initially missed because the patients are first examined in a specialist department for skin, eye, joint, or other focal lesions, without radiographic examination, and the usual general well-being of the patient may be deceptive.   Bodley-Scott (1938) found 9 per cent. sarcoid appearances among 300 lymph nodes excised for enlargement suggestive of

Hodgkin's lymphadenoma; he himself saw 8 cases in less than a year. Our third plate here illustrates cryptic cases which clinically suggested traumatic or tumour conditions. Diagnosis is essentially histological, with radiographic verification.

DISCUSSION

We have here an example of that rare combination, tuberculosis and sarcoid changes, rare in the sense that tubercle bacilli were recovered by culture in a sarcoidosis patient, for one of the salient characteristics of sarcoidosis is the difficulty with which tubercle bacilli or any other criteria of the infection can be demonstrated. Around this difficulty has centred the main discussion about the nature of sarcoidosis. Is it an atypical form of tuberculosis or is it a disease *sui generis* with clinical and histological features resembling tuberculosis? Its usual slow development and long benign course, its tendency to spontaneous regression, and especially the possibility of its attacking almost any organ and tissue of the body have led to its description under many names, and it is only within comparatively recent years that a unified conception has emerged. The idea of a tuberculous causation is still, however, received with reserve by many observers.

The present case is of importance, showing as it does the coincidence of tuberculous disease and sarcoid lesions. The essential question to be considered is, therefore, how far can the clinical and pathological data be correlated to support the thesis of a single underlying disease process?

The history is a long one, covering a period from the initial disturbance at the age of five years to her death in March 1946 at the age of nineteen and a half. Signs and symptoms varied during this long period. Some lesions, such as the iridocyclitis and splenic enlargement, improved and disappeared; others, like the joint affection, the kidney lesion, and the slight, irregular, varying temperature, remained more or less constant.

The literature on sarcoidosis is now extensive, but, in brief, the disease may be described as a systemic lesion, a reticuloendotheliosis with the formation of a·folliculoid tissue, affecting particularly the lymphoid and hæmopoietic tissues, with pathological changes in excess of the clinical manifestations. The organs specially involved are lymph nodes, lung, bone-marrow with osteoporotic (pseudocystic) changes, spleen, liver, eyes and, in about 50 per cent. of cases, the skin; but, as already mentioned, no tissue is immune. The various lesions occur in conjunction or in succession, and there is a marked tendency to regression with residual fibrosis. There is even a possibility of complete quiescence with restoration of normal structure. Such a disease will obviously produce a varied clinical picture, and it is not surprising that it has been described under many names according to the organs and tissues most affected. It seems now

to be generally accepted that Boeck's sarcoid, lupus pernio, some other cutaneous tuberculides, osteitis tuberculosa multiplex cystoides, uveoparotitis and Mickulicz's disease, and possibly Still's disease, are probably all manifestations of the same condition, though in the majority of cases definite proof may not be forthcoming. Though most of the recorded cases of sarcoidosis which were followed for a period of years eventually succumbed to frank tuberculous disease, proof of the presence of that disease in the early and intermediate stages was not obtained. In recent years a more detailed and critical analysis of the available data has strengthened the view that sarcoidosis is, in reality, atypical tuberculosis of "chronic miliary" or "non-caseating" type, and this assumption, even in the almost invariable absence of the ordinary laboratory and clinical criteria of the disease, is strongly supported by the rare cases in which tubercle bacilli are recovered. Pinner (1938) was able to find in the literature only twenty-five records of bacteriologically positive cases. The number of completely convincing positive results is, he finds, insignificant.

The findings in this present case are therefore of great interest. They differ in a number of respects from those of a previous and perhaps more characteristic case described by us in 1942, where the diagnosis of sarcoidosis rested on the lung X-ray appearances which underwent progressive clearing, and on microscopical examination of spleen and liver tissue removed at operation. Both eyes in this case were also involved but the skin escaped. Since this case was published the patient has passed without mishap through pregnancy and parturition, and later enquiry shows her to be in apparently complete health ten years after the appearance of her first symptoms. Evidence of the tuberculous nature of her condition was never very convincing. There were negative Mantoux and animal tissue inoculation tests and sputum was not available for examination.

The present case is definitely one of combined pulmonary tuberculosis and sarcoidosis of other tissues proved histologically in excised skin and lymph glands. We shall discuss the various manifestations in detail.

JOINTS.—In a number of cases reported as sarcoidosis or as non-caseating tuberculosis, involvement of serous surfaces—synovial, pleural, pericardial, and peritoneal—has been described. The following cases are illustrative. A male patient of Mellon and Beinhauer (1937) aged eighteen years, had low-grade apical lung tuberculosis without demonstrable tubercle bacilli in the sputum, widespread lymphadenopathy, scattered skin lesions of sarcoid structure, and fusiform swellings of both knees and fluctuating enlarged bursae at both wrists without X-ray evidence of bony change. Swollen ankles in a patient of thirty-one years with sarcoid lymph nodes and bilateral lung X-ray stippling were associated with urinary symptoms in a patient described by Horton et al. (1938); tubercle bacilli were not recovered from the sputum of this patient and the Mantoux test was

negative. The combination of chronic multiple arthropathy with enlarged lymph glands, though clinically not suggestive of tuberculosis, calls for radiographic and other investigation as a possible chronic miliary form of this disease.

The sarcoid condition of bone which produces the cystic osteoporosis shown by X-rays postulates a hæmatogenous spread to bone marrow, but in some of the joint lesions reported no evidence of X-ray change was found in the underlying bones. The condition in them was apparently entirely articular and probably synovial in origin, with fluid formation. Bodley-Scott (1938) mentions the knee joint as a site of sarcoidosis, and we have examined tissue from the prepatellar bursa area (Figs. 10, 11) in a patient of thirty-five years.

In our patient the joint swellings decreased after the last carious teeth were removed, but they did not disappear, and as sarcoidosis is characteristically regressive or stationary for considerable periods there was no necessary connection with the oral sepsis. Bilateral involvement of joints is not suggestive of the usual tuberculosis picture, but if infection be blood-borne the actual sites may be more or less accidental and as difficult to explain in their location as are hæmatogenous tumour deposits. The fact, however, remains that simultaneous bilateral lesions of knees and ankles are not suggestive of any form of tuberculosis, and Loewenstein's views (1944) on the tuberculous nature of some cases of rheumatoid arthritis are not generally accepted.

Since Poncet and Leriche published their book in 1909 there has been much controversy on the subject of tuberculous rheumatism. It is probable that views on this subject in this country require revision, for the joint affections which they described were of a rheumatoid type and were not the destructive arthrites of tuberculosis which are so often monarticular lesions. The subject has been recently reviewed by Seligson (1945) and Sheldon (1946). Poncet and Leriche described three types. The first type, the arthralgic, is well-known to most tuberculosis workers, for an appreciable percentage of tuberculous patients give a history of " acute rheumatism " before the onset of the organ tuberculosis. This rheumatism is characterised by its evanescence, its lack of joint swelling, and its complete disappearance. In Type 2 the joints are actually swollen and painful and are indistinguishable from acute rheumatic fever joints. This type is often associated with involvement of serous cavities, particularly the pericardium, and is little, if at all, influenced by salicylates. These two types need not concern us further, but the third, or chronic rheumatoid type, requires consideration. This type is not common, but Sheldon, (loc. cit.), described one case in a female child of seven with fusiform swellings of both wrists, both knees, and the left ankle, all of which were slightly painful and had restricted mobility. The joint condition was associated with enlargement of glands in axillæ and groins and with slight enlargement of the spleen. A month after she came under his care typical abdominal glandular and plastic tuberculosis developed. Final recovery took place with persistence of slight swelling of the

affected joints, all of which, however, with the exception of the wrist, recovered full mobility. It is very rarely that tubercle bacilli are isolated from these joints, although that has been described. Weissenbach (1933) described a chronic polyarthritis, diagnosed clinically as rheumatism, in which tubercle bacilli were isolated and cultured from the synovial fluid. The histological appearances of excised synovial membrane differ from those of progressive tuberculous lesions chiefly in the absence of giant cells. That lays the whole contention open to doubt if we continue to think in terms of a bacillary condition. In discussing the pathology of these lesions Sheldon quotes Coburn in the following statement : " If the development of rheumatic fever is associated with an abnormal immune response of the host, we might expect to find comparable disease syndromes following other acute infections. Such a syndrome should not appear where there is an overwhelming virulent infection nor in the highly immune host. It should be found among the intermediates. In our opinion, comparable phenomena do occur in tuberculosis and syphilis."

It is unfortunate that we were not given permission to take biopsy material from a joint in the case of our patient and that a post-mortem examination could not be made. We have therefore no proof of the nature of the joint affection, but, clinically, it fits into our conception of a protracted tuberculous infection which started with pains of a myalgic or arthralgic type, passed to the development of relatively painless rheumatoid joint swellings and from that to a very chronic, fibrotic lung tuberculosis and disseminated lesions which histologically deviated from the typical progressive tuberculous type to the non-caseating sarcoid type.

SPLEEN.—Occasional enlargement of the spleen was noted during the early illness in the Sick Children's Hospital at five years of age. It was sufficiently evident to suggest the possibility of Still's disease, but this diagnosis was discarded because the type of joint lesion present did not support it. There was also an increased hilar shadow at this time. No later clinical observations on the spleen are available, but it was not palpable at any time while she was under our care.

The cause of this early and varying splenomegaly is doubtful, but as it was an evanescent phenomenon, and as splenic enlargement is common to many diseases, including tuberculosis and sarcoidosis, it need not engage us further.

HEART.—The heart condition was congenital and had no apparent connection with any of the other lesions.

LIVER.—The liver became palpable at fifteen years of age and slight varying enlargement persisted until her death. By that time lung fibrosis was well established and it is difficult to attach very special significance to the enlargement.

EYES.—A bilateral iridocyclitis, diagnosed clinically as tuberculous, appeared at fourteen years of age, but subsided, with improvement of

vision, during the following year. Recurring attacks of iridocyclitis are common in the sarcoid state and tuberculosis is an undoubted cause of certain forms of iridocyclitis. It would be unwise to draw diagnostic conclusions from the unexpected improvement which took place in her case. That may be left as a recorded fact.

THE BLOOD.—The blood picture at fifteen years, with a total red cell count of 5¼ millions, indicates a slight polycythæmia, probably associated with the other congestive features and possibly with the advancing lung fibrosis. The white cell count was also slightly raised, but the percentages lay within normal limits and there was no monocytosis. Three and a half years later the red cell count had risen to over six millions and the differential white cell count showed a mild polymorphonuclear leucocytosis, but again no monocyte increase.

In many reported cases of sarcoidosis and non-caseating tuberculosis the blood picture has shown little deviation from normal; in others the blood counts are not given. Pinner (1938) mentions cases with polycythæmia and cyanosis following fibrosis of the lung with emphysema, but in our case the cardiac condition is a complicating factor. Monocytosis, a variable and perhaps over-emphasised diagnostic finding in sarcoidosis, is considered by most observers to indicate a phase of active extension of the disease represented by a temporary monocyte increase in the blood as well as by the formation of new folliculoid endothelial tissue. A monocytosis may therefore depend on the time of blood examination in relation to an active phase; it may be absent or it may rise to over 20 per cent.

Blood Sedimentation Rate.—This has remained between 30 and 40 and throws little light on the complex clinical picture.

KIDNEYS.—Albuminuria, with some granular casts, was present on admission to the sanatorium at fourteen years of age. There were no symptoms of nephritis. A few months later she had an attack of hæmaturia and a little pus appeared in the urine, but the slight leucocytosis (9400) showed no differential diagnostic features, and tubercle bacilli were not found on culture of the urinary sediment. Fifteen months later, in March 1943, after a sudden urinary tract exacerbation, albuminuria increased and there was persistent slight pyuria, but again tubercle bacilli were not found. The slightly raised urea concentration in the blood noted in February 1945 suggests some chronic interstitial lesion in the kidney rather than parenchymatous involvement and before death there was a persistently high blood urea level.

As noted in the clinical history, it is difficult to fit these urinary findings into the general picture. Acid-fast bacilli, morphologically resembling tubercle bacilli, were found in the urinary sediment on one occasion, but cultures were twice negative. In view of the widespread lesions present in lungs, lymph nodes, and skin, it is possible that renal tissue was also involved, with the formation of small foci of hæmatogenous disease. Schaumann, Crosnier, and others mention

sarcoid lesions in the kidney, associated clinically with albuminuria and hæmaturia and represented histologically by an interstitial folliculoid cell proliferation similar to appearances seen in skin and lymph nodes. Were the condition here part of a hæmatogenous tuberculosis of a low grade of activity or of a sarcoidosis, the failure to demonstrate the bacillus would accord with the usual negative results of examination of skin and lymphoid tissue. Horton *et al.* (*loc. cit.*) describe a case of "sarcoid type of non-caseating tuberculosis," showing anergy and monocytosis and involving skin, lymph nodes, lung and bones; autopsy revealed a more extensive spread, including foci in renal tissue. Pinner (1937) found kidney involvement in a case of Boeck's sarcoid with other visceral foci.

LYMPHOID TISSUE.—Enlargement of the *spleen* in the initial stages of the illness at five years of age has already been noted. The *tonsils*, which Schaumann considered a helpful diagnostic tissue in sarcoidosis, were removed before fourteen years and no histological report was available. There was widespread involvement of *lymph nodes*, first noted at fourteen years, when radiographs showed a mass in the right lung root associated with the pulmonary tuberculosis. Three years later, during routine examination, groups of large, soft, painless, mobile nodes were found in axillæ and groins. The appearance of the lungs at this time suggested a sarcoid condition and histological examination of excised axillary nodes showed a picture characteristic of sarcoidosis (Figs. 3-7). Enlarged nodes were also found five months later in the left deep iliac and right epitroclear regions. Later microscopical examination of another axillary node confirmed the previous appearances.

The hilar node enlargement may have been associated with a primary tuberculous lung infection but the lymphoid masses in other areas need explanation. Various observers have noted the absence of regional relationship of enlarged nodes to skin lesions in sarcoidosis; the skin of the trunk, for example, is usually unaffected, but axillary nodes are frequently enlarged. This and the widespread adenopathy suggest a mainly hæmatogenous rather than a lymphogenous spread and support the opinion that sarcoidosis is a disease of chronic miliary, hæmatogenous distribution. Diffuse lymph gland enlargements of this type are well known in tuberculosis. The explanation of the failure to find tubercle bacilli in these sarcoid glands may well lie in the time at which search is made. Kyrle's work (1921) on cutaneous sarcoidosis with acute exacerbations showed that bacilli were present only during the earliest phases of dissemination, and this may be generally true for all tissues affected (see p. 472).

THE PRIMARY FOCUS OF THE DISEASE.—Though a diagnosis of pulmonary tuberculosis was first made at eight years of age, an increased hilar shadow was present at five years when the patient first came under observation. After eight years of age she had persistent cough, and by fourteen years the lung picture suggested a

chronic fibrotic type of tuberculosis. Radiographically the appearances then were those of a chronic fibrotic tuberculous lesion of the right upper lobe, and there were in addition diffuse abnormal shadows in both lungs of the sarcoidosis type. We discussed in our previous paper the possible relationship of these lung appearances to chronic miliary tuberculosis, especially of the lymphogenous type, and the differentiation between the two conditions is often a matter of personal opinion. The absence of glandular enlargements in the lung roots is thought to be against a diagnosis of sarcoidosis, but on other grounds the two conditions may be indistinguishable. Dr Saffley in fact considered that the shadows in this case were those of chronic miliary tuberculosis.

Chronic miliary tuberculosis is a well-defined clinical entity and the condition has been fully described by Hoyle (1938) and Hoyle and Vaizey (1937). It is interesting, in reviewing the literature of this condition and of sarcoidosis, to notice the descriptive over-lapping. What one writer describes as chronic miliary tuberculosis may to another be sarcoidosis, and what a few years ago was the former is now more often considered to be the latter. Hoyle (1938) writes of chronic miliary tuberculosis: "About half of the patients show evidence of dissemination of the disease to other organs than the lungs. Such general dissemination is shown clinically by enlargement of the spleen which occasionally is extreme, by a general lymphadenitis, by a tuberculous arthritis, or by involvement of the urinary system or skin or eyes. Exceptional complications are the cystic affections of bones known as osteitis tuberculosa multiplex cystoides, polyserositis, uveoparotitis, Addison's disease and purpura. As a rule, lesions disseminated in this fashion take the chronic pattern of the original disease in the lungs unless the meninges become involved. . . . Wide-spread, even generalized dissemination of miliary foci may, however, occur sometimes in a recurrent way and yet the meninges apparently escape. . . . It is evident that the clinical features of chronic miliary tuberculosis are deceptive, not only because they often appear to be trivial but also because they can be polymorphic. . . . Although the radiographic appearances (lungs) as a rule are so like those of acute miliary tuberculosis, in a minority of cases they are entirely different. There are enough records to show that these atypical appearances are still due to miliary disease, but it is a lymphogenous as distinct from a hæmatogenous form. . . . In such lymphogenous examples of the disease the mediastinal lymphatic glands are involved, so that abnormalities of the mediastinal shadow are likely to be found." He states further that the chief difficulty in diagnosis is to obtain satisfactory proof of tuberculosis, and he records the fact that even in cases where the diagnosis is not in doubt the tuberculin reaction may be negative. In discussing the differential diagnosis from sarcoid lesions, he comments on the great difficulty in distinguishing the two conditions, especially as the skin may be involved in chronic miliary

tuberculosis. "Present evidence," he adds, "would suggest that sarcoid conditions may well be tuberculous, at any rate so far as the lesions in the lungs are concerned." Much of Hoyle's description might be applied to the accepted clinical conception of sarcoidosis which has now firmly arrogated to itself the uveoparotid syndrome, the lymphadenopathy, the chronic splenomegaly, and the cystic osteitis. The latter, in fact, is now considered to be diagnostic of sarcoidosis. One is on safe ground in stating that clinically the two conditions may be indistinguishable, and the differentiation depends upon histological examination.

DISSEMINATION.—Apart from the atypical joint condition at five years, the first manifestations of disease after the diagnosis of lung tuberculosis were the skin lesions which appeared on the lower limbs at the age of nine. Their histological nature was not determined at that time. When fourteen years old, both eyes became involved, and a profuse culture of tubercle bacilli was obtained from sputum. Shortly afterwards there was an attack of hæmaturia, and during the next year, at the age of fifteen, the liver became enlarged. The condition of the joints remained unchanged and the albuminuria persisted. At the age of sixteen and a half she had an attack of right renal pain associated with pyuria. Two months later the skin rash appeared. Lymph node enlargement appeared at seventeen years and further node involvement later in the same year. Tubercle bacilli were again found on culture, this time from gastric lavage. The nature of the skin condition, sarcoid in distribution in that it was mainly limited to face and limbs, was now confirmed histologically.

In addition to these localised foci of disease there was also the systemic disturbance, manifest in under-development in size and weight and the absence of secondary sexual changes. This may have been related to the congenital cardiac condition but it is difficult to dissociate it from the disseminated disease lesions. Congenital hyposecretion of the anterior lobe of the pituitary gland causes infantilism ("the pituitary dwarf") and sarcoidosis of the pituitary gland has been noted by several observers (Schaumann, Bodley-Scott, Hannesson), with autopsy verification, but there was no indisputable clinical evidence of pituitary involvement in this case. Her appearance suggested that the congenital cardiac lesion was responsible for the failure of development, but that is an open point.

THE RELATIONSHIP OF TUBERCULOSIS AND SARCOIDOSIS.—The essential interest and importance of sarcoidosis lies in its relation to tuberculosis. Many sarcoid cases fail to produce during life convincing laboratory evidence of tuberculous infection, and the absence of this evidence, combined with the clinical picture of comparative well-being in spite of widespread foci of disease, has prevented or delayed the recognition of sarcoidosis as a possible atypical form of tuberculosis. There

is now, however, a growing recognition of an underlying identity, and cases such as the one now reported, in which tuberculosis of the lung, proved by culture and animal inoculation, is associated with a sarcoid condition of skin and lymph nodes, though rare, are obviously of great importance. This point is emphasized by Pinner (1938) after an exhaustive examination of the literature. The later fatal and frank tuberculous condition of many reported sarcoidosis cases does not, however, necessarily postulate an identical initial causation of the two diseases, a question we refer to later.

In discussing the relation of sarcoidosis to tuberculosis, it is helpful to look at the problem in general terms rather than to focus attention on the more distinctive features of the two diseases. " Typical tuberculosis," clinically and pathologically, presents little difficulty in diagnosis. In sarcoidosis, description has tended perhaps to rigidity, with emphasis on negative findings which differentiate it from tuberculosis—the usual absence of general disturbances even with extensive pulmonary involvement, the absence of tubercle bacilli, the negative Mantoux reaction, and histologically, little or no caseation necrosis, little surrounding lymphocytic cell reaction and few or no giant cells—but we would suggest that these features have been overstressed, and that as in other diseases there is a wide range of variation in any series of cases, many of which may lie within the diagnosis of either sarcoidosis or tuberculosis. Where the two lesions co-exist it is appropriate to note points of similarity.

(a) *The Pattern of Disease Distribution.*—This is much the same in sarcoidosis and hæmatogenous tuberculosis, with lung, lymph nodes, spleen, liver, bone marrow, skin, and eye showing the most frequent involvement. Miliary tuberculosis, acute or chronic, may affect any organ or tissue, and this finding is also brought out in autopsied cases of sarcoidosis where more widespread lesions are found than are clinically apparent.

(b) *The Formation of Similar Folliculoid Tissue.*—The micro- and macroscopical appearances in sarcoidosis, " monotonously uniform " (Pinner, 1937), are described in numerous reports in the literature and are illustrated here and in our previous study of the condition (1942). There is rarely difficulty in recognising tuberculous tissue histologically, but intermediate pictures between it and sarcoidosis are found. The latter shows, in general, more evenly cellular follicles, with few or no giant cells, little or no caseation, and a varying but usually sparse lymphocytic cell reaction, but, as in tubercle, diffuse areas of endothelioid cell proliferation may be formed. As in tubercle (Innes, 1937) also, the classical picture may be characteristic only for certain stages of the disease. The conception of an essential dissimilarity is largely undermined by the experimental production, by infection of tubercle bacilli, in animals like the white rat which have a high natural resistance to the tubercle bacillus, of sarcoidosis tissue almost identical with that of Boeck's disease in humans (Jadassohn,

1932 ; Gloyne and Page, 1923). Some individuals have " a sarcoidal form of reaction " to the bacillus (Volk, 1913).

(c) *The Absence of Convincing Features differentiating Sarcoidosis from Tuberculosis.*—Chronic miliary tuberculosis, first described by Adami in 1910, is a recognised form of the disease. In studying descriptions and recorded cases of the condition (Hickling, 1938; Hoyle, 1938 ; Hoyle and Vaizey, 1937), it is difficult to find any features, clinical, radiographical or histological, which point to an essential difference between this form of tuberculosis and sarcoidosis. The resemblance, indeed, seems so close that, as we have already stated, cases reported as chronic miliary tuberculosis suggest sarcoidosis to other observers, and the difficulty of differentiation is increased in " unusual cases " (Davidson and Ellman, 1941), where, in those described as similar to chronic miliary tuberculosis, the sputum has remained free of bacilli and the lung mottling has gradually cleared, with residual fibrosis. In sarcoidosis the Mantoux test is rarely positive on early examination, but later it may become positive, 'as, for example, when the skin lesions disappear (Whittle, 1936). The absence in sarcoidosis of tubercle bacilli in sputum may be explained by the peribronchial and perivascular spread of an interstitial lesion in the lung, with slow fibrosis instead of caseation necrosis and vascular damage. But this usual development does not rule out such activation of the disease as would produce the ordinary tuberculous picture.

(d) *The Development of Sarcoidosis into Tuberculosis.*—This has been regarded, especially by earlier observers, as a *post hoc* development in lung tissue damaged by fibrosis and hyaline change, *i.e.* an added late complication, without necessary implication of a causal connection between the two diseases. This is an argument difficult to support or refute in the frequent absence of data from long observation of cases and autopsy examination. Certain facts, however, suggest that the connection between sarcoidosis and tuberculosis is more than merely *post hoc* or accidental. The clinical course in sarcoidosis is characteristically long and indolent, and complete recovery, even with restoration of tissues, is possible. In fatal sarcoid cases death may be due to cardiac failure associated with pulmonary impairment, or to localisation of the disease in a vital organ or to extensive destruction of hæmopoietic tissue (Schaumann, 1924 ; Tillgren, 1937); but the most frequent cause of death in recorded cases is a frank tuberculosis. Is this a new infection or the activation of a long present, smouldering one ? Beinhauer and Mellon (1938) explain the development of non-caseating into classical tuberculosis by the transformation into the acid-fast Koch bacillus of " non-virulent, non-acid-fast dissociants of the tubercle bacillus recovered from lesions indistinguishable from Boeck's sarcoid," a position which has not received general support. It is unnecessary as an explanation in our case, as extensive sarcoid involvement was associated with the recovery of ordinary human tubercle bacilli from sputum. Many explanations of the latent or

smouldering stages of tuberculosis have been suggested, such as the small number of infecting organisms, their fluctuating virulence and the fibrous encapsulation of the diseased areas, but these are all really included in the conception of natural variations in the reaction of the host tissues in which the organisms lodge. The time interval between infection and patent disease is rarely known. It seems, therefore, very difficult, if not impossible, to draw a sharp distinction between the two diseases, as their differences may be only those of degree, not of kind. Pathologically, most if not all of the differences can be explained by the acceptance of sarcoidosis as a non-caseating form of tuberculosis in individuals with high immunity and low sensitivity. Continued quiescence or activation with the production of the ordinary tuberculous picture depends on the maintenance or the loss of stable balance between host and parasite.

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NOTES, CLINICAL AND HISTOLOGICAL, ON ILLUSTRATIONS

FIGS. 1 and 2.—The patient, aged nineteen years, showing (*a*) joint swellings of the lower limbs ; (*b*) cutaneous sarcoidosis most marked on limbs and face and (*c*) general underdevelopment, with bulbous finger tips.

FIG. 3.—*Axillary lymph node.* Biopsy tissue showing diffuse hyperplasia of small folliculoid type with very few giant cells ; no caseation necrosis. 6975/44. ×50.

FIG. 4.—*Same tissue*, with giant cells of varying size but with no definite relation to folliculoid structure. ×90.

FIG. 5.—*Same tissue*, showing a giant cell and a small follicle side by side. The former has an " inclusion body " of unexplained origin. ×375.

FIG. 6.—*Same tissue*, with giant cells and endothelioid hyperplasia without follicle formation. ×200.

FIG. 7.—*Same tissue*, with small non-caseating follicles and giant cells of varying size. ×300.

FIG. 8.—*Skin.* Biopsy tissue from sarcoid lesion on flank, showing characteristic endothelioid strands with rare giant cells and sparse lymphocytic cell reaction ; no ulceration. 9670/45. ×90.

FIG. 9.—*Skin.* A deeper area of the same lesion, showing extension of sarcoid tissue into the subcutaneous fat. ×130.

FIGS. 10-14.—The sarcoidosis picture in clinically cryptic tuberculous cases.
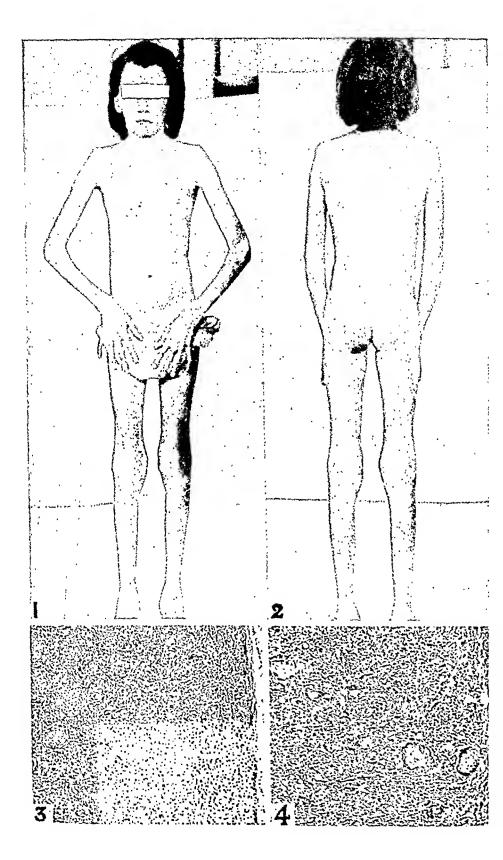
FIG. 10.—*Tuberculous bursitis.* Woman, aged thirty-five, complained of swelling over left patella, three months' duration ; slight trauma to knee eighteen months previously ; a little intermittent pain, no limitation of movement. On examination, fluctuant swelling, no effusion into knee joint. Patient healthy with no sign of tuberculous disease ; no radiograph. At operation, thickened, nodular prepatellar bursa, very adherent to surrounding tissues ; removed ; wound healed well. No later notes obtained. Showing elongated folliculoid formations with a few giant cells ; no caseation necrosis. 8239/45. ×90.

FIG. 11.—*Same tissue*, with rounded follicles and some giant cells ; no definite caseation. ×140.
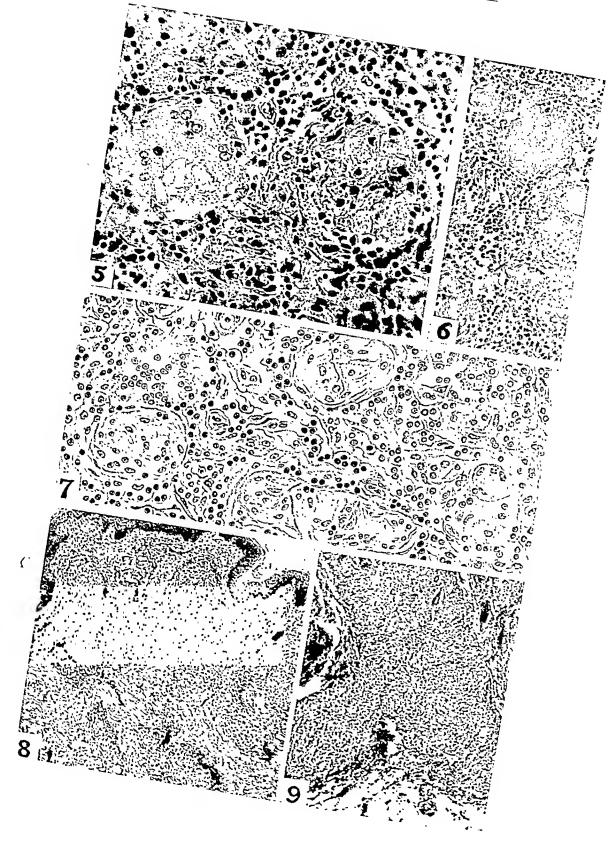
FIG. 12.—*Mammary carcinoma.* Married woman, aged fifty-six, with painless swelling of breast for six weeks, increasing in size ; clinically, doubtful carcinoma of breast and axillary lymph nodes. Showing minute non-caseating follicles with some giant cells ; malignant tissue and stroma infiltrated with lymphocytes. Lymph nodes showed no carcinoma but only an early tuberculous infection. The mammary tissue suggests a hæmatogenous tuberculous involvement. 7148/41. ×150.

FIG. 13.—*Tissue excised from parotid area*, clinically parotid adenoma, man, aged fifty-seven. Histologically, sarcoid lesion, apparently in pre-auricular lymph node, with irregular strands of endothelioid tissue. No giant cells or caseation. Suggestive of uveoparotitis or of Mikulicz's disease (parotid and lachrymal gland swellings). Patient epileptic and in hospital for this three years later. Recent examination showed a few palpable lymph glands in both groins and one at the angle of the right mandible ; no positive radiographical evidence of a tuberculous lesion, but generalised emphysema, some thickening over the right diaphragm and opaque areas of doubtful significance in the periphery of the right upper lung. No iritis, no bony changes in the hands, no spleno- or hepatomegaly. 8296/43. ×60.
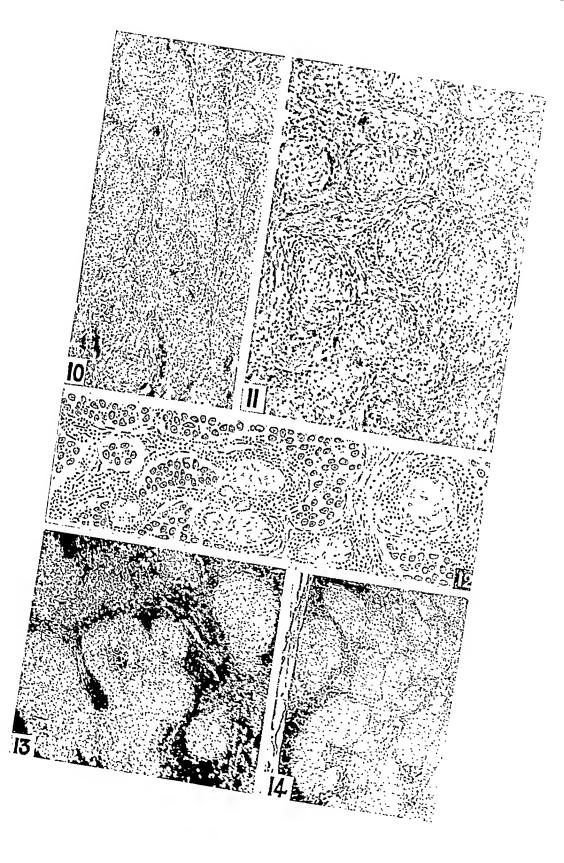
FIG. 14.—*Lymph node.* Biopsy tissue ; no history available except enlargement. Showing the " hyperplastic adenitis " of Ewing, which he identified with Adami's " paratuberculous lymphadenitis." 4561/31. ×50.

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SOME OBSERVATIONS ON FUNCTIONAL HEART DISEASE *

By IAN G. W. HILL, C.B.E., M.B., F.R.C.P.Ed.

(1) INTRODUCTION.—There is a natural tendency in undergraduate teaching to concentrate on cases exhibiting signs and symptoms of valvular or coronary disease to the neglect of the functional case. The neurotic tends to be dismissed as such, or to be referred for psychotherapy at other hands. It is perhaps not sufficiently emphasised to students that the diagnosis of functional heart disease forms an important part of the duty of every doctor. The psychiatrist can be of the greatest assistance in the analysis of the patient's temperament and personality, and in his treatment, but the assessment as to whether or not given symptoms have an organic basis is a matter for the physician. Adequate study of the clinical aspects of functional cardiac cases and their differentiation from the organic are, therefore, important.

By contrast with the organic case, the individual suffering from imaginary heart disease is spared the progressive deterioration to terminal failure with pain or congestion, but he may have his activities severely restricted by his symptoms. Not only is this to his economic detriment, but in addition he often suffers mental torment through fear. To the laity, heart disease connotes short days and a dramatic exitus. The sufferings of the *malade imaginaire* are real enough ; the repercussions on himself, and on his relatives and dependants, are matters of fact, not fancy.

The frequency of functional cardiac cases is considerable. White [7] found that 10 per cent. of 3000 cases referred as heart disease were functional, exclusive of the 2 per cent. of organic cases who showed a functional overlay. General experience confirms this high figure, both in private and hospital practice. One was impressed by the frequency of such functional cases while working in association with Dr Rae Gilchrist from 1937-39 on cases of angina pectoris at Edinburgh Royal Infirmary, and during the war years one has seen a great number of cases under the label " Effort Syndrome."

(2) MATERIAL.—(*a*) Cases from civilian practice and from the Royal Infirmary collected during 1937-39. During the investigation of some 200 cases of true angina, some 150 cases of innocent precordial pain were encountered. (*b*) In the army, three series of cases from Britain and the Middle East, totalling almost 500, have been analysed. An early attempt to split these into groups (effort syndrome, cardiac neurosis, etc.) was abandoned. Clear-cut cases of one or other may

* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 5th December 1946.

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be found, but there is too great an overlap in the average case to permit of accurate classification.

TABLE I

492 Cases of Effort Syndrome—Age Incidence; Length of History, etc.

		Series I. U.K. 1940.	Series II. M.E.F. 1941-42.	Series III. U.K. 1943.
Total cases		50	241	101
		Per cent.	Per cent.	Per cent.
Age-groups . .	Under 20 .	4	0·25	2·0
	20-29 .	74	70·9	41·5
	30-39 .	14	24·0	47·5
	40-49 .	8	4·5	8·0
	Over 49 .	0	0	1·0
Type of enlistment .	Regular .	..	15·6	3·0
	Reservist .	...	3·0	5·0
	Territorial .	...	13·4	9·0
	Volunteer .	...	32·8	13·0
	Conscript . .	...	35·0	65·0
Length of history .	Under 1 year	30	48·0	23·0
	1-3 . .	16	22·0	19·0
	3-10 . .	24	13·7	21·0
	Over 10 .	30	15·2	37·0

(After *The Lancet*, 1945, ii, p. 161)

The reasons for considering that this is not primarily a service condition will be apparent from Table I, where it is shown that in a large proportion of cases the onset of symptoms antedated entry into the service. For example, in early 1940 when the war was but a few months old, 70 per cent. of cases seen had had symptoms for over a year. In the later series in 1941-42, and in 1943, 29 and 55 per cent. respectively had had symptoms for over three years. In the three series of cases, from 15 to 37 per cent. had had symptoms for over a decade. As one has said elsewhere, these cases are unmasked, rather than produced, by service conditions. This view was also held by Lewis.[6]

(3) SYMPTOMATOLOGY.—The symptoms commonly encountered and their frequency are set out in Table II. They may be divided into two groups :—

(a) Symptoms which are found commonly in organic disease.

(b) Symptoms not usual in cases of organic disease.

Dealing first with the latter, it is important to realise that symptoms of this group are not usually indicative of heart disease. Giddiness, exhaustion, etc., may be due to many causes, some affecting the circulatory system, but are not characteristic of organic heart disease, especially when they occur in young subjects.

Symptoms of group (a), breathlessness, pain and sometimes palpitation, are common in cases of true heart disease with limitation

of the cardiac reserve. The differentiation of the dyspnœa and pain in functional and organic cases, however, can be accomplished in most cases.

A complaint of breathlessness, for example, may on analysis prove to be the patient's expression for a respiratory tic, for deep irregular sighing breathing occurring in the course of otherwise normal respiration. Even when associated with increase in rate and depth of respiration, it does not show the close relationship to work done noted in cases of cardiac failure. It may be provoked only by specific (often distasteful) acts, or by acts associated with a fear of straining the heart, or it may be produced by the slightest exertion

TABLE II

492 Cases of Effort Syndrome—Incidence of Individual Symptoms

	Symptom.	Series I.	Series II.	Series III.
		Per cent.	Per cent.	Per cent.
a.	Dyspnœa	70	86·5	84
	Pain	58	82·5	85
	Palpitation	74	80·0	72
b.	Giddiness	24	31·5	30
	Headaches	8	22·5	16
	Syncope	2	12·5	16
	Exhaustion	20	17·5	17
	" Nerves "	6	16·5	16
	Sweating	2	5·0	6

in patients displaying none of the objective signs of right or left heart failure. The following case illustrates the point :—

CASE I.—Sgt. T., aged 32 years. On examination for entry to Territorial Army in July 1939 was diagnosed as " rheumatic mitral stenosis : fit for sedentary occupation in Pay Corps only." Despite a careful examination in September 1940 in which it was noted that he had an evanescent precordial systolic murmur, with normal X-ray and normal electrocardiogram, he was later admitted to hospital by a senior dental officer for extraction of a tooth " as this N.C.O.'s heart condition renders the administration of a local anæsthetic impossible." When seen in March 1943, he had been referred for invaliding out of the army.

He had rheumatic fever at 21, and was in bed for eight weeks. Before this he had been a keen athlete (hammer-throwing, weight-putting, etc.).

His main present complaint was dyspnœa, especially severe on rising in the morning. This was sometimes so extreme that he required help when shaving. He was breathless on the slightest exertion. Palpitation occurred both on exertion and at rest in bed, keeping him awake. He described a burning pain ." behind the sternum " (*sic*), which lasted up to a week at a time. When pain was present he could swallow only slops.

On examination, very tall (6 ft. 3½ in.) and thin ; apprehensive ; but keen to remain in army and do his job. Heart clinically not enlarged ; apex in fifth space less than 3 in. from mid-line ; tachycardia with over-active sounds. Loud obtrusive high-pitched late mitral systolic murmur, clearly following a

closed first sound, and disappearing on holding the breath; no diastolic murmurs. X-ray of heart normal. No disease of lungs, blood, etc.

The patient was reassured, and regraded to a *higher* medical category as part of the reassurance.

A case with organic disease, with dyspnœa of such intensity and such limitation of effort, would have displayed clear-cut signs of congestion and cardiac enlargement.

The pain in functional cases seldom bears any close resemblance to that of true effort angina. It tends to be referred to the left breast, or below it, or around the nipple; it is rarely felt in the midline. It does not show the usual radiation to the arms, though it may shoot up to the shoulder or round to the back. It is described by a variety of adjectives, as dull and aching, or as soreness, icy coldness, heaviness, or dragging, or alternatively as a shooting, stabbing or pricking pain. It does not bear the unmistakeable stamp of coronary ischæmia—the gripping or strangling sensation in the middle line. It is pertinent to recall that Heberden in 1768 said of the latter " the seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris." " Angina pectoris " means a " strangling of the breast," not merely a pain in the chest.

The duration of the pain in functional cases is variable: aching pains are said to last hours or days; sharp stabbing pains may be momentary. But the classical story of a few minutes of steady pain as encountered in angina of effort is not given.

The effort relationship is not clear-cut as it is in organic cases of myocardial disease. Pain in half the cases comes on at any time, independent of effort, even while in bed; or it may be felt on performing some specific trivial act, though absent on more strenuous exertion.

CASE II.—Wm. B., aet. 39 years. " Strained " his heart four months before being seen at R.I.E. on 30th October 1937. Since then had had precordial pain on exertion or bending. In an exercise test he climbed and descended steps equivalent to a vertical height of 75 ft. in less than two minutes, without production of pain, though it made him breathless. He later developed pain after bending a few times to touch his toes.

In assessing whether pain in a given case is of organic or functional type one must remember that true anginal pain may be felt in unusual situations, for example, in the left or right arm, or in the back or upper abdomen. In such cases the chest may be free from pain till later in the attack, or till later in the course of the disease. More rarely one meets with a functional case in which the history closely simulates that of ischæmic pain, as for example :—

CASE III.—Mrs M. W., aet. 39. She had had rheumatic fever at age of 16 years, with no residual valvular lesion. Seen in September 1937, she gave a history of pain during the last few months, starting in the middle line and radiating to the middle of the left arm, and described as " crushing."

The pain, however, was not related in any way to effort, and often came on when she was sitting quietly by the fire. It was found that her aunt, whom she nursed, suffered severely from angina, and actually died in an attack in her chair by the fireside while her niece was with her. The niece's attacks had developed since then. She admitted that her symptoms were exactly like those of her aunt, and that she was terrified she might have the same disease.

Patients whose presenting symptoms are typically functional in character may have a concomitant organic lesion. (Three per cent. of White's series of over 2000 organic cardiac cases.[7]) Thus it is fairly common in cases of early mitral stenosis to find dyspnœa out of proportion to the stage of the lesion and to the state of the heart, associated often with stabbing or aching pain in the chest, or with undue fatigue, etc. Such patients usually know that they have an organic lesion, and ascribe their symptoms to it. Again, patients who have weathered a coronary occlusion may on return to active life develop precordial aches and pains of functional type, probably through fear of recurrence and increased consciousness of their hearts.

The handling of such "mixed" cases offers a pretty problem in wise management, steering between the shoals and quicksands of undue caution and unjustifiable licence.

(4) ÆTIOLOGY.—The various predisposing and precipitating factors found in the army series are shown in Table III.

TABLE III

492 Cases of Effort Syndrome—Summary of Etiological Factors

		Series I. U.K. 1940.	Series II. M.E.F. 1941-42.	Series III. U.K. 1943
Total cases		50	241	101
		Per cent.	Per cent.	Per cent.
Remote previous illnesses	Rheumatic fever . .	14	10·8	17
	"Rheumatics" . .	18	4·5	6
	Other illnesses as child .	23	12·4	30
	"Nervous" as child .	4	7·6	...
"Doctor-made"	Alleged VDH . .	2 } 38	8·0 } 30·6	17 } 52
	Alleged "strained heart" .	12	6·0	6
	Vague statements .	24	16·6	29
Precipitating factors	Act of physical strain .	10	8·0	6
	Overwork . . .	...	2·0	1
	Blitz experiences . .	6	4·5	11
	Recent infections . .	12	20·0	6
	"Trauma"; ops., heat, etc.	4	...	...
	Home worries . . .	...	11·0	11
No precipitating factor found: "inadequate type"		24	24·0	30

(After *The Lancet*, ii, p. 161)

Recent infections may be the precipitating factor in some cases. In our series, such were relatively uncommon (6-20 per cent.) by comparison with the last war experience of Lewis,[3] of Krogh, Ritchie and White [2] and of Hume.[1]

CASE IV.—Pte. J. W., aet. 23 years. Had diphtheria in November 1941; symptoms appeared during convalescence and prompted his reference for examination. No previous significant illness. Complaint of trivial pain behind sternum, breathlessness on exertion, palpitation on exertion and at rest. No other symptoms. Tall, well-built lad; no evidence of cardiac disease; tachycardia. Reassured. Treated with graduated physical training. discharged to full duty after fourteen days, fit.

In a large group, remote previous illness, often in childhood, has been the starting-point of a physical inferiority which has persisted through life. In many cases the original disease was *rheumatic fever*. Lewis [4] found in 1914-18 that some 23 per cent. of effort syndrome cases had a history of rheumatism or chorea. In our three series from 15 to 22 per cent. had a history of old " rheumatism," including from 10 to 15 per cent. with definite rheumatic fever. None of these had clinical evidence of old endocarditis. Since from 11 to 30 per cent. of our cases had a similar history of severe *non-rheumatic illness* in childhood, it is probable that the later disability in these cases was due not to rheumatic carditis, but to over-protection by relatives of a child who was physically weakened by his illness.

CASE V.—Sig. M. B., aet. 22 years. Patient said he had three " heart attacks " before he was ten. At the age of ten he had rheumatic fever; thereafter had only wind enough for swimming or cricket. Symptoms had persisted for twelve years. He fainted on an exercise, and spent three and a half months in hospitals and convalescent depôts before reaching our centre. He complained of dragging pain below the left breast, momentary, brought on by exertion; also of moderate breathlessness; and slight palpitation. A short lad of slight build, he was intelligent but unhappy. There was marked tachycardia (120), but no other abnormality on physical examination. He was reassured, treated with graduated physical exercises, and discharged to full duty five weeks later. Good result.

CASE VI.—Dvr. C., aet. 29 years. Patient stated that his trouble started eighteen years before, when he was twelve. He fainted at a " school treat," and was afterwards seen by a specialist at a London teaching hospital, who is alleged to have told his mother not to worry, but his heart was weak. He was advised to take up a light job, and forbidden to play games of any kind.

The patient had always been delicate. He was in a Sanatorium when he was six, and attended an open-air school for six years, where he " did a lot of gardening but had little learning." From five to eleven years of age he had attended an M.O.H. Clinic in a London borough every six weeks. His mother always attended the Clinic with him. He said he had always been very nervous, scared of other boys, and had no friends in school or army. He had never wanted to play games.

His complaints were of fainting attacks, giddiness and headaches for eighteen years and of night-blindness. Physically, tall and well-built, he was extremely nervous. There was no clinical evidence of heart disease ; his blood pressure was 200/95, falling in a few minutes to 180/90 ; there was no evidence of coarction of aorta.

Disposal ; referred to psychiatrist.

In a considerable number of cases in civil practice, the onset is related by the patient to a *specific act of physical strain*, or to a blow over the heart. On closer analysis, many complaining of symptoms alleged to have started after a specific act have in reality had symptoms for months or years.

CASE VII.—Pte. S. P., aet. 24 years. Had had symptoms for eight years when seen at the end of 1941. He gave a history of " strained heart " in July 1940, while lifting a 2 cwt. concrete block from a lorry. The Medical Officer put him on light duty for three months, and thereafter he worked in the cookhouse. He had never done full duty since, though he went to the Middle East in March 1941 and served in Tobruk for several months during the siege till he was evacuated with sand-fly fever, and then referred to our centre.

He had had jaundice at the age of sixteen, and the family doctor was alleged to have stated his heart was affected. He was laid up for six months on account of his heart then, and had never played games since. Previously he had played football for his county.

His complaint on admission in 1941 was of pain from the sternum round to the left axilla, dull, toothachy with occasional stabs, and lasting a few minutes. He was dizzy on bending. Tall and spare, he showed no clinical evidence of heart disease. He responded very poorly to physical rehabilitation, and was transferred to a neuro-psychiatric wing of the hospital.

This question of " heart strain " is further discussed below.

Psychological Group.—It may be contended with some justification that all functional cases depend on a psychological abnormality. But the term is used here to specify those cases in which the onset was palpably related to such psychological disturbances as worry over family matters, personal frustration or overwork, or reaction to disembarkation for service in a distant tropical country, or reaction to war experiences of shelling, bombing, etc. It also includes cases in whom an obviously inadequate personality lay behind the development of symptoms ; these, together with physically inadequate types, formed at least one quarter of all our cases.

CASE VIII.—Sig. K. B., aet. 20 years. Had had symptoms for six years. An illegitimate child, he was left by his mother when eighteen months old. He left school early (13½) and had had a hard life. He apparently made good, and had recently become engaged. He had been happy enough until shortly before admission, when he became very worried, since his mother had attempted to trace him for her own ends. The man with whom she was living having developed diabetes, she was destitute and had turned to her deserted son for

support. He had no love for his mother, and resented her claim upon him. He had played games normally at school, but was a clerk in civil life.

He complained of stabbing pain below the left breast, coming on at any time while walking, swimming, sitting at his desk or lying in bed. The pain lasted ten to thirty minutes, and radiated to the left rib margin. He was breathless on exertion, and on sitting up in bed, and with the pain. He had palpitation on effort and at rest. He was giddy when the pain came on.

On examination, he was of average height, good muscular development, anxious and shy ; he had no cardiac abnormality. He did not respond to simple physical training, and was eventually transferred to the care of a psychiatrist.

CASE IX.—Pte. R. R., aet. 23 years. Duration of symptoms ten years, worse for the last two. He had pleurisy at the age of thirteen, and had since suffered from hay fever and tightness in the chest. He was able, however, to play football at school. At the age of fifteen and a half he had to leave school. Although he was apparently quite a bright scholar and had hoped to take up a skilled career, his father's death had rendered it imperative that he should earn his living at once. He frankly admitted that he was depressed at his missed opportunities. He had been subjected to considerable bombing in France in 1940, and again at Mersa Matruh and Moascar in 1941. His symptoms had been worse since those experiences.

He complained of a jagging, momentary pain in the left breast, coming on at any time. He had occasional dyspnœa and was much troubled with palpitation and giddiness. Physical examination showed him of average build and physique. There was no abnormality in the heart. He was not specially anxious to serve, and disliked the army. Rehabilitation by physical training failed completely, and he was transferred for psychotherapy.

" *Doctor-made* " *Factor*.—It will be apparent from several of the case histories already related that in many the patient quotes a doctor as supporting the diagnosis of heart disease. In Case VII, for example, a patient was told on two occasions by different doctors that he had heart disease, when in fact the heart was healthy. Other examples may be quoted :—

CASE X.—Pte. A. F., aet. 20 years. Had had symptoms for six years. He had pneumonia after a scout camp at age of fourteen, followed by pains in the legs. He was kept in bed by his doctor and seen by a noted cardiologist, who is alleged to have said, " Take things easy, and it will come all right if you look after yourself." He had a recurrence of muscular rheumatism in 1938 and again in January 1940, when he was referred to hospital after two weeks in bed. As a youngster he had played games, swimming particularly, but was easily made breathless. His civil occupation was a grocer.

He complained of tightness in the left breast after physical training, great breathlessness on exertion, and dizziness after exertion. A well-built and intelligent lad, he was anxious to serve. There was no clinical enlargement of the heart ; a pulmonary systolic murmur, soft and probably functional, was present but no evidence of cardiac disease.

The patient had been eighty days in hospitals before he was referred to us. He was immediately placed on a P.T. course after strong reassurance, and nineteen days later was discharged for duty. Before discharge, he had passed

through a gruelling " passing out " test, including strenuous P.T., football, courage exercises over a horse, and running 1 mile. The patient was seen again three years later at a hospital in the Middle East suffering from malaria. He had done two years' strenuous campaigning in a field ambulance in the Western Desert.

CASE XI.—Pte. O. R., aet. 23 years. Had had symptoms for six months. At twelve years of age he was run over and got pneumonia. At age of sixteen, after strenuous P.T. he got a severe pain in the chest and his doctor told him he had " strained his heart." He was kept in bed six or seven months and recommended rest for two years. He had never played games since.

He complained of ache and suffocating pain " over the heart," lasting two to five minutes, brought on by exertion. He had breathlessness on exertion and with the pain. He also had palpitation and said his worst complaint was insomnia.

A Eurasian, he was well built, anxious and depressed. There was no clinical enlargement of the heart or other abnormality in circulatory or in other systems. He was diagnosed by the psychiatrist as a chronic anxiety state, based on an unstable temperament, and was transferred to a psychiatric centre for treatment.

The patient with pain at his heart (or where he imagines his heart to be) fears he has heart disease. Every act or word of the examining doctor, a shake of the head, a thoughtful look, a half-hearted re-assurance, is twisted by the patient to mean the worst—" My heart *is* affected." Patients' statements as to what their doctors said, categorical and dramatic as they often are, must be swallowed with a bushel rather than a grain of salt, but even a doctor's simple advice " to take things easy " and prohibition of games and such like, make deep impressions. An extravagant sentence to six months in bed and two years' rest, such as was recounted above, is an experience which leaves its mark for life on the strongest patient.

In one-third to one-half of the cases, the patient stated that a doctor or doctors at one time or other had told him or his parents that his heart was abnormal. Other factors may play a part in individual cases, but surely the repetition of the same story in such a large proportion is no mere coincidence. In many cases, cardiac neurosis is frankly " doctor-made "; in others, the medical statement is quoted by the patient as evidence to support a claim to special treatment, or to bolster up his self-respect when he finds himself incapable of leading, in war or peace, the ordinary life of his fellows.

(5) THE RÔLE OF THE DOCTOR in management of such cases is frequently difficult and always highly important. One may profitably survey the doctor-patient relationship in these cases from both angles in turn.

The patient's outlook is noteworthy in all cases of this type. First in importance is the recognition that *fear* plays a dominating part in his reaction—fear of heart disease, of sudden death, of the unknown. His emotional response to a diagnosis or even to a suspicion

of heart disease is intense, and is coloured by this over-riding fear. The patient tends in his anxiety to exaggerate simple statements made by the doctor, and may appear deliberately to twist an innocent remark into a veritable death sentence. The patient who inwardly fears that he has heart disease is ready to accept a diagnosis confirming his fear, and once he has become convinced that his heart is in fact diseased, later reassurance as to its integrity may prove singularly ineffectual. Convictions of heart disease, based originally on a sharp pain in the breast and reinforced by a chance word in a doctor's surgery, may prove ineradicable in later years.

In some cases, the diagnosis of heart disease or "weak heart" may provide an obvious prop to a psychologically or physically inadequate patient, may serve to shield him from the buffets of life, may procure him the attention he craves or may provide adequate excuse for failure in his work or play. Yet in the majority of instances fear remains the predominant emotional colour in the reaction of these patients to a diagnosis of heart disease.

From the doctor's viewpoint, the welfare of his patient, as always, comes first. The conscientious practitioner is anxious lest, by permitting over-activity, he should contribute to shortening the days of the victim of valvular disease or myocardial weakness. The tendency is to err on the safe side, to limit exercise excessively and in doubtful cases it may be needlessly. One tends to over-protection of the heart damaged by valvular lesion and to treat as evidence of true myocardial damage any sudden precordial pain arising during effort. Some discussion on these two points may, therefore, be appropriate.

(a) *Management of Early Valvular Disease.*—There is abundant evidence that the subjects of early valvular disease, rheumatic or congenital lesions, are not harmed by fairly strenuous exercise if within their limits of tolerance. In the absence of marked cardiac enlargement and/or signs of venous engorgement, and provided there is no evidence of *active* rheumatic carditis, such patients should not be unduly restricted in their work or play. One is familiar with individuals who have carried on actively throughout a fairly long and useful life despite a valvular lesion. One public school housemaster, dying after a short illness in his late forties, had for many years walked and climbed extensively in Switzerland and had thrice climbed Mont Blanc despite his aortic stenosis. If such is the case in firmly established cases of valvular disease, how little excuse is there for prohibition of games and advocacy of the sedentary life to those who have a murmur which is at most suspicious of a valvular lesion. For the large class of patients with completely innocent murmurs, often of exo-cardial origin, no limitation whatever is justified, and to them the very existence of their murmur should not be made known. In deciding for or against organic disease and limitation of effort let the size of the heart and the signs of venous congestion be the guides, rather than the quality and propagation of a systolic murmur.

(b) *Cases of " Cardiac Strain."*—The effects of hard physical effort on the heart were analysed by ·Lewis.[5] He pointed out that when a skeletal muscle is over-loaded, the strain· falls directly on its fibres, which may rupture, but that the only strain on the heart in strenuous effort is indirect, and is imposed by maintaining output against a raised blood pressure. No direct load can fall on the cardiac muscle fibres, except in the rare event of rupture of an aortic valve cusp. Such an accident is rare in any case, and in healthy hearts extremely rare ; the ruptured cusp is practically always the seat of disease, usually syphilitic. The physical signs are striking and pathognomonic.

Sudden pain in the chest during lifting or straining at a load is not due to rupture of myocardial fibres, but to other factors—tearing of skeletal muscle in chest wall or pectorals, etc. ; or more rarely, to myocardial ischæmia, an effort angina. This last is easily recognisable by the features of the pain in site, character, duration, etc.

The decisive moment for good or ill in the management of a case of either type is at the end of the first examination of the patient by his own doctor. A direct statement that the heart is diseased or strained, or an implication to that effect by look or deed, will remain indelibly impressed on the patient.

It is urged that a thorough examination be carried out at the first interview and particularly that a careful history be taken ; that the doctor reach certainty in his own mind as to the diagnosis ; that he weigh the pros and cons most carefully before committing himself, and that before the patient leaves the surgery he should be firmly reassured in cases without lesion, or given reasonable advice in cases where future limitation of effort is judged necessary. Temporising is not permissible, unless at the end of a short period of observation a definite and wholly confident opinion as to his condition can be given to the patient.

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DISCUSSION

Dr Traquair, in declaring the paper open for discussion, referred to the masterly manner in which Dr Hill had presented it. He was himself personally interested in it as practically everything Dr Hill said was analagous to ophthalmic conditions. Every ophthalmic surgeon was familiar with the patient who has been told not to use his eyes and who goes about afterwards in fear of blindness.

Dr Hewat expressed the thanks of the Society to Dr Hill for his excellent address. He had given them food for thought in various directions and shown the necessity for psychiatric co-operation of the highest order in dealing with these cases. He recalled an interesting experience he had during the last war, while at Colchester with Dr Lewis, watching the efforts being made to get this effort-syndrome put right.

Dr Hewat also referred to an interesting letter in the *Lancet*, which he afterwards discovered was written by the late Dr James Miller, giving a most vivid description of functional disturbances from time to time after coronary thrombosis.

It was only information, such as Dr Hill had given them from his wide experience both in civil and army life, that would help them in their dealings with such cases as he described.

Dr Baldwin remarked that he was particularly interested in the " doctor-made " cases. While he believed that in many cases the patient invariably misquoted the doctor in his statements, it was important that the doctor should be careful not to give by signs or half-hearted reassurance that there might be a cardiac lesion. Dr Hill's warning was a very sound one on this point.

Dr Malcolm Smith referred to the legal aspect of the functional heart in compensation cases, and the difficulty involved in deciding such cases by the lay element.

Dr Morison was interested to know if Dr Hill, in his experience of patients who had had amoebic dysentery, could tell him whether this functional condition of the heart was likely to follow the administration of emetine.

Dr Douglas Robertson was of the opinion that the condition was of main interest to the general practitioner rather than to the consultant. It was better dealt with by the patient's own doctor as the fact of bringing in a consultant was apt to give rise to a cardiac neurosis. It was the duty of the general practitioner himself to decide whether the patient had an organic or functional disorder. Dr Robertson was interested in Dr Hill's reassurance that the case with an organic lesion of moderate degree is able to undertake a reasonable amount of exercise and also to engage in ordinary employment. He quoted a case he came across recently of an elderly man who had been told that his heart was seriously damaged and who had remained strictly in bed for seven years. Dr Robertson examined him carefully and found nothing organically wrong with his heart—he was now doing a job in spite of having been in bed for seven years.

Dr Wilkie Millar agreed that the condition was one of primary importance to the general practitioner. He referred to the academic side—the teaching of students in the wards. It was important that they should be trained in diagnosing the functional from the organic.

Dr Hill in his reply said he was greatly interested in the analogies drawn by Dr Traquair and Dr Hewat to cases of similar " doctor-made " type as encountered in ophthalmological practice and in cases of respiratory disease.

He agreed with Dr Eason that these patients were often really ill, and that the individual patient required study before treatment could be effective. Thus investigation of such a case demanded the exercise of patience and the expenditure of much time, often up to an hour for each patient.

With regard to Dr Somerville's remarks that a poisoned heart might be more readily strained, Dr Hill reminded the meeting that in practice it was frequently an intercurrent infection that precipitated an attack of congestive failure in an ambulant patient with a known *vitium cordis* but little disability.

Dr Malcolm Smith had raised the medico-legal aspect of such cases. Dr Hill said that a patient might develop severe symptoms after a specific act which might render him unable to earn his living. In such cases, even if an organic lesion had been excluded, Dr Hill believed the man was entitled to some compensation. The legal aspect of this belief he must leave to others better qualified to judge. As in all similar cases, the sooner such a claim was settled the better for the patient.

Dr Eason had asked how such cases were to be managed in peace-time practice. Dr Hill admitted that it was much easier to treat effort syndrome cases under service conditions, in squads progressing from stage to stage of rehabilitation. The men were encouraged by their progress, reassured that no harm would result by seeing their colleagues doing strenuous exercises, and developed a healthy competitive spirit. In handling a single individual in private practice all these advantages were lost. It was a sound rule, however, once the patient had been thoroughly examined, to refrain from any subsequent examination of the heart. Re-examination tended to undermine confidence. Even taking pulse rates repeatedly was ill-advised : the tachycardia should be ignored and dismissed as not significant. A metaphor sometimes useful was to compare the heart to a watch : the regulator might make the hands go fast or slow without the main-spring being affected. So in the heart, a fast pulse did not mean the cardiac pump was seriously impaired.

Dr Morison had asked whether these cases might not occur as a sequel to emetine poisoning in the treatment of cases of amœbic dysentery contracted in the East. Dr Hill said that he had only once seen a case of possible emetine myocarditis, despite the large numbers of cases of amœbiasis treated. In Burma at one time over 600 cases per month were being evacuated with this disease. He quoted an instance of a special column returning from a long jungle patrol with 33 men who had all had a complete series of ten daily emetine injections *on the march* without ill-effects. Such heroic measures were not to be recommended, but the incident did show that toxic effects from emetine were not very common.

In closing, Dr Hill agreed with Dr Robertson that the diagnosis and management of these functional cases were primarily the responsibilities of the general practitioner. That was why he had chosen this subject for the paper to which they had given so courteous a hearing.

EAR-PIT (CONGENITAL AURAL AND PRE-AURICULAR FISTULA) *

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CONGENITAL aural fistula is a relatively rare deformity. Bezold (1885) and Urbantschitsch (1877) estimated its frequency at 0·19 per cent., and Eyle (1891) at 0·26 per cent. Rugani (1910) quoted a much higher figure, and apparently the frequency may rise to 5 per cent. in a small community which includes several affected families. Pathologically there is nothing and surgically there is little of interest in the anomaly, but its illustration of certain genetic principles is illuminating, the understanding which it affords of the development of the pinna is valuable, and the contribution which it may make to chronic inflammations of the face is occasionally important.

The affection was first described by Heusinger in 1864, and Virchow in the same year and Urbantschitsch subsequently speculated upon its possible origin from the first branchial cleft or the cleft between mandibular and maxillary processes. The first English description (apart from a translation of Urbantschitsch's paper) was that of Sir James Paget in 1878.

CLINICAL APPEARANCE.—The ear-pit is a narrow, blind fistula, as a rule a few millimetres deep (Gradenego, 1893 ; Marx, 1926), and will accommodate the lead point, and the point only, of a finely sharpened pencil. It may be unilateral or bilateral, and sometimes two or more pits occur together in the same ear (Fig. 1). Multiple pits may rarely communicate with each other (Schuller, 1929), though it is suspected that in such cases the communication is effected only by suppuration. Rarely also does a pit communicate with a branchial fistula (Thollon and Labernadie, 1919). The areas in which the pit may be found are indicated in Fig. 2. (1) The commonest site of those which become infected and require treatment is *pre-auricular*, in a roughly triangular area based on the anterior border of the attachment of the auricle, and narrowing to an apex which lies on the line from the tragus to the angle of the mouth. They seldom lie more than an inch in front of the tragus. The truly auricular varieties are (2) *anterior (marginal) helicine*, on the ascending limb of the helix, which includes 90 per cent. of all these fossæ (Congdon et al., 1932) ; (3) *crural*, in the crus helicis, recorded once by Schwabach (1879), and eleven times by Congdon ; (4) *posterior helicine*, on the

* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 5th December 1946.

postero-lateral aspect of the descending limb of the helix, and illustrated only by five of Congdon's subjects, one of whom, a Chinese girl,

FIG. 1.—Combination of unilateral anterior helicine and infected pre-auricular fistulas in a girl of nine years. The child's father, and one younger brother, present unilateral anterior helicine fistulas in precisely the same situation and on the same side.
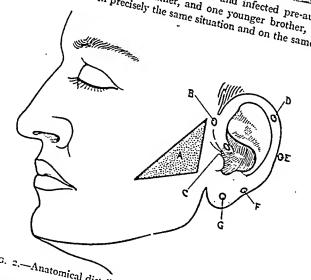
FIG. 2.—Anatomical distribution of ear-pits, after Congdon.

presented two posterior helicine pits in the same ear; (5) *helico-lobular*, very rarely recorded (Hahne, 1889, and Breuer, 1927); (6) *central lobular*, on the medial or on the lateral aspect of the lobule, or on

both (Sabrazes, 1890 ; Fischer, 1903 ; Jenks, 1916 ; Edmonds and Keeler, 1940), and rarely piercing the entire thickness of the lobule (Bland-Sutton, 1887) as for an ear-ring ; (7) *post-auricular*, close to the root of the ear, and recorded only rarely (Battle, 1905, and Hadda, 1909). A pit or fossa has been described once in the floor of the inferior articular (triangular) fossa (Congdon, 1932), once in the concha (Caldera, 1872), and once in the antitragus (Dyer, 1885).

It should not be assumed that every pit or fossa in the pinna is congenital. Artificial pits can be treated by children addicted to ear-picking, and this explanation should be considered especially if a pit or fossa is found in an unorthodox situation. Acquired pitting is common in the lobules of those races who practise the ear-piercing of the newly-born.

The orifice of a congenital ear-pit is usually tiny in size, and either circular or lentiform in outline. The track is straight and can be conveniently probed by a bristle. It is lined by squamous epithelium only (Grunert, 1898 ; Steiner, 1925 ; Breuer, 1927), though rarely an island of cartilage may be present in its wall. The epithelium may be folded and valvular, and sometimes a tiny diverticulum branches from the lumen. The direction of the track varies with the situation of the fistula. A bristle introduced in a pre-auricular fistula passes backwards, inwards and slightly upwards towards the helix; the fundus of the anterior helicine variety lies almost immediately below its mouth ; the crural track lies along the line of the crus, and the other varieties are usually directed medially. In a unique example observed by Fournier (1919) the track passed through the parotid gland and coursed downwards to open again on the skin surface just below and behind the angle of the mandible, but in this case it is presumed (Congdon) that a true pre-auricular fistula had acquired a connexion with a cavity derived from a branchial groove or pouch. In no instance has a true pre-auricular or auricular fistula been shown to communicate with the external meatus ; one fistula, described by Virchow (1864) did communicate with the external meatus, but it is doubtful whether this particular example was a true pre-auricular fistula.

On the skin of the cheek, below and in front of the orifice of a pre-auricular or anterior helicine fistula, there may be a curious area of patchy scarring of the skin, elongated from above downwards and likened by Streeter to striæ gravidarum in miniature. The scarring may be superficial to the deeper part of the track or may lie in front of the position of the fundus, showing no relation whatever to the track. This scarring appears in an illustration in the paper of Stammers (1926) who ascribes it to suppuration in the deeper part of a pre-auricular fistula, but it has been observed even in early infancy, when suppuration has not had time to become established, and Heusinger (1864) recorded its symmetrical bilateral occurrence in front of marginal helicine sinuses.

A pigmented mole, often tiny, is not uncommonly detected in front of the fistulous opening, and a few centimetres from it.

Only occasionally does stagnation of inspissated sebum occur, sometimes with the production of a musty odour unpleasant to the patient, sometimes with suppuration, recurrent abscess-formation, facial œdema, and, exceptionally, the appearance of secondary fistulæ.

RELATION TO OTHER ANOMALIES.—In a demonstration of congenital deformities of the face at the Royal College of Surgeons of England in 1909, Sir Arthur Keith illustrated the concurrence of pre-auricular fistula with cleft palate, spina bifida, and imperforate anus. Other deformities of the ear—accessory auricle, partial absence of the auricle, and incomplete development of the ear in its various degrees—may be associated with congenital fistula. The vast majority of instances more recently reported, however, particularly those described by anatomists and geneticists, have occurred in otherwise normal people. Congdon and his fellow-workers found only two associated abnormalities of ear or face in 518 Asiatics and white and coloured Americans who presented congenital aural fistulæ. The fistula itself is rarely the subject of a surgical consultation, while any associated abnormality often is, and the association therefore seems frequent to the surgeon.
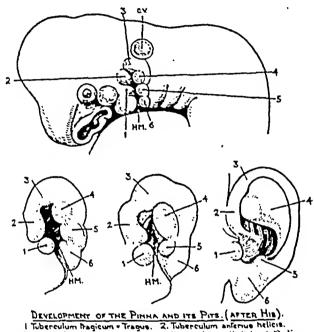
The simplicity of the defect is so absolute that it is difficult to recollect any pathological structure of less complexity, unless it be absence of an organ or of part of an organ, yet similar fossæ elsewhere in the body are not numerous. The rare mucous pits of the lower lip, situated on its buccal aspect and usually bilateral, are identical in structure ; they are said to be due to incomplete fusion between tuberculum impar and the mandibular processes. The pits of the upper lip which are sometimes associated with cleft palate and seem to be due, like hare-lip, to non-fusion of the philtrum and the maxillary processes, are similar also, as are the rare fistulæ of the columella.

DEVELOPMENT OF THE PINNA.—The pinna develops around the dorsal extremity of the first branchial cleft (Fig. 3). Its first appearance was described by His (1885) as of six low hillocks or tubercula, separated from each other by shallow depressions. The first two tubercula lie on the branchial edge of the first arch, the third embraces the extremity of the first cleft, and the fourth, fifth and sixth arise from the cranial margin of the second arch. Streeter (1922) describes two hillocks, 6 and 6,' in the position of the sixth tubercle of His. Knowledge of the contribution made by each individual tubercle to the fully-fashioned auricle is still inexact and incomplete. According to His, the first to sixth tubercles fuse to form respectively the tragus, the crus helicis, the helix, the antihelix, and antitragus and the lobule, but Wood-Jones and I-Chuan (1934) mention a remarkable instance of complete absence of the structures derived from the first arch, in which the pinna lacked only its tragus, so that the arrangement

and development of the pinna from the tubercles perhaps does not conform to the original description of His.

DEVELOPMENTAL ORIGIN OF EAR-PITS.—There are three main hypotheses of the method of origin of auricular fistulas.

(1) *The Intertubercular Hypothesis of His.*—Since the time of His, ear-pits have been generally assumed to originate in the grooves between the six primary tubercula, but high modern embryological authority is opposed to this hypothesis. G. L. Streeter (1922) in a classical study of selected specimens of the developing ear, observed that the tubercles of His are shallow, rudimentary, and evanescent,

DEVELOPMENT OF THE PINNA AND ITS PITS.(AFTER HIS).
1 Tuberculum tragicum = Tragus.   2. Tuberculum anterius helicis.
3 Tuberculum intermedium helicis   4. Tuberculum anthelicis = Anthelix.
5 Tuberculum antitragicum = Antitragus. 6. Tuberculum lobulare = Lobule.
HM. Hyomandibular cleft.   OV. Otic vesicle.

FIG. 3.—Development of the auricle, after His.

disappearing soon after their formation, and replaced by a one-piece primitive embryological ear ; he challenges the importance of the tubercles in pinna development, too, by citing their occurrence in reptilian and avian embryos, which do not develop an external ear. Wood-Jones and I-Chuan agree with Streeter's estimate of the un-importance of the tubercles of His, and conclude that " the hillocks are of such low elevation that it is hardly possible to conceive of a pit or fistula being formed at their sites " ; they assume therefore that ear-pits take origin from unenclosed portions of the first branchial cleft itself.

. (2) *The Branchial Hypothesis of Virchow.*—Virchow reported one fistula of obvious branchial origin, but the track in this instance opened superficially in the region of the angle of the jaw, and subsequent writers have hesitated to include Virchow's fistula in the auricular

and pre-auricular categories. Most authorities agree that a branchial origin can hardly be assumed for pre-auricular and anterior helicine tracks which run downwards and forwards, separated from the external meatus (first branchial cleft) by the whole thickness of the tragus. The line of the fistula is parallel and cephalad to the line of the first cleft. Pre-auricular fistulæ never communicate with the external meatus as they might be expected to do if they took origin from the first cleft, and they do not lie between tragus and lobule, which is the line of the cleft. Frederici (1930) has recently applied the branchial hypothesis to marginal helicine sinuses, but to these only.

(3) *The Facial Cleft Hypothesis.*—From time to time it has been suggested that pre-auricular fistulas are due to partial failure of fusion between maxillary and mandibular processes, but if this were so, they might be expected to be distributed more evenly along the facial line of fusion. The only sinus which I have found in the literature on this line anterior to the " pre-auricular field " outlined in Fig. 1 is that described by Schwendt (1890)—a sinus surrounded by a congenital scar lying 3 cm. posterior to, and 5 mm. below the angle of the mouth ; this might properly be assumed to be maxillo-mandibular in origin.

Thus apparently the least objectionable hypothesis is that of an inter-tubercular origin for auricular and pre-auricular fistulas. Stated in its widest terms, this hypothesis implies the inclusion of the groove between two tubercles when the tubercles fuse, or the inclusion of part of the angle between the base of the tubercle and the adjacent skin. Even if accepted, however, this hypothesis does not explain the quite considerable distance which may separate the fundus of a fistula (which usually lies close to the attachment of the pinna) from its cutaneous orifice. Streeter has suggested that the direction and the occasionally substantial length of a pre-auricular fistula may be explained by the growth of the mandibular process, which stretches the overlying skin and carries the mouth of the fistula downwards and forwards—the usual inclination of the track. A similar upward stretching of the skin, accompanying the growth of the cranium, would explain the direction of the anterior helicine fistulas. The fixation of the fundus might be explained by a close attachment of ectoderm to mesoderm at the bottom of each groove.

The scarring of the skin of the face, nearly always on a line from the orifice of the fistula to the point of the chin, with its striæ at right angles to that line, has been similarly explained by Streeter. The failure of adjustment between ectodermal and mesodermal growth which has produced the fistula has been associated with a failure of ectoderm to adjust its growth to that of the underlying mandibular process (or cranium), and the overstretched ectoderm has scarred. (Pinkus in 1927 described a similar congenital scarring of the skin in front of the thigh.) Further, not infrequently, pre-auricular fistula is associated with so-called accessory auricle—the little polypoid masses of cartilage, like displaced

portions of tragus, which may hang or protrude from the skin in front of and below the external meatus; growth of the mandibular arch has overstretched the superjacent ectoderm and a portion of the first tuberculum has been distracted from the main mass of the tragus.

Fig. 4 shows an incompletely developed auricle, in a child four years of age, which seems to cast a substantial light on the development of the auricle and on the origin of ear-pits. (An almost identical deformity is illustrated in Schwartze's text-book.) Some of the elements of the distorted pinna are difficult to name, for the external meatus may be either of two tiny pits, but these definite statements seem to be justified :—(1) the tragus and the crus helicis are absent; (2) the lobule is well-formed, and above it a well-marked eminence represents the antitragus; (3) the antihelix ascends from the antitragus and is attached to it at its edge, but is partly separated from its main mass

FIG. 4.—Deformed and partly deficient auricle in boy of four years. Two views of a plaster cast. A cartilage graft has been inlaid in the subcutaneous tissues as a preparation for subsequent plastic reconstruction. Detailed description in text.

by a deep groove ; (4) the upper end of the antihelix is free, and bent backwards on itself like a closed fist, its curved extremity enclosing a deep pit ; (5) the antihelix is separated by a deep groove from the helix ; and (6) the helix is curved on itself too, like a fresh-sprouting bean, attached by a narrow base and its curved extremity bowing towards the antihelix. The individual parts of this defective auricle might be interpreted otherwise than I have interpreted them, but it is difficult, in viewing its parts, not to read in them the third, fourth, fifth and sixth tubercles of His. The deformity, indeed, could almost be deduced from the original diagram of His.

Even if some other explanation than a tubercular origin of the pinna be advanced to explain this deformity, the illustrated specimen shows that, in a deformed auricle if not in an auricle otherwise normal, pits may arise by two separate mechanisms :—(1) by failure of fusion of tubercles or other component parts of the auricle ; and (2) by folding of each component part on itself. Incipient pits are discernible in the folded " helix," between " helix " and " antihelix," and between " antihelix " and " antitragus " ; the folded extremity of the " anti-

helix " encloses a fully-formed pit. For completeness it should be added that a flat pigmented mole, 2 mm. in diameter, lay 3 cm. in front of the midpoint of the auricular prominence.

INHERITANCE OF EAR-PIT.—Ear-pit is inherited as an incomplete dominant of variable manifestation, and without sex difference (Connon, 1941). That is, the tendency to suffer from ear-pit is dominant to the tendency not to suffer from it. There are thus, in any affected family, considerable numbers of affected individuals and the variety continues through many generations. Subjects who inherit the tendency to the deformity need not always develop it in the same degree (variable manifestation). The majority of the members of an affected family who suffer from the tendency to ear-pit manifest the typical lesion which I have described. Some, however, show a more severe deformity, and a few will have a gross abnormality such as partial or complete absence of the auricle; at the other end of the scale, some affected members will have a scarcely perceptible ear-pit, and a few will show no defect. There is, indeed, some evidence that the genetic factor is not alone concerned in the genesis of ear-pit; McDonough (1941) has recorded uniovular twins, only one of whom suffered from ear-pit; the other had normal auricles, but his son was born with a pre-auricular fistula. From this non-concordance of identical twins it can be concluded that, while the tendency to ear-pit is inherited as a dominant, its variable manifestation can hardly be due to a genetic factor (Quelprud, 1940), but must depend upon pre-natal environment, using the term environment in its widest sense.

A curious feature of the inheritance of ear-pit, recorded by Edmonds and Keeler (1940), is that in the unilaterally affected members of any given family, one side, the right or left, is more frequently affected than the other.

SURGERY OF EAR-PIT AND PRE-AURICULAR FISTULA.—Uncomplicated ear-pit does not require treatment.

The complications of pre-auricular fistula have already been mentioned, but they are so rare that the routine excision of uninfected fistulas should not be recommended. Once infection occurs, any acute abscess should be opened. Even after successful drainage, however, infection once established is likely to recur until the whole fistulous track is eradicated.

It should be remembered that infection or ulceration may be more obvious than, and may occur at a considerable distance from, the mouth of the fistula which is responsible for it. This is particularly true if the mouth of the fistula is completely blocked. Any cellulitis or abscess formation in the pre-auricular area should inspire a search for the orifice, perhaps partly occluded, of a pre-auricular fistula. A recurring ulcer in front of the ear, even though unaccompanied by signs of infection, may be due to fragility of the dermal scarring which may accompany a fistula, even though the orifice of the fistula is unobtrusive and distant.

ACKNOWLEDGEMENTS

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DISCUSSION

Dr Traquair referred to the fact that in hereditary eye conditions where there was one deformity, there was usually another, whereas this condition of the ear was an isolated deformity. He was interested to know whether there was any sex incidence.

Dr Scott stated that these cases usually came to hospital on account of the deformity of the ear, with a view to their appearance being improved by plastic operation. The hearing appeared to be of secondary consideration.

Where the meatus was too narrow to allow of examination of the ear, X-ray might be helpful in deciding whether the middle and internal ears were developed. These patients may show complete absence of external ear, or vary from one extreme to the other—where no external ear at all is present to where the external ear is developed and there may be odd accessory auricles or nodules.

Dr Martin referred to the fact that it was difficult to be certain that this condition was always developmental and not the result of some injury in childhood, or an infection of the auricle. In adults the presence of acne in the ear very often gave rise to a condition almost identical with small " ear pits."

In his opinion the condition was fairly common but rarely recognised as a congenital defect.

It has been suggested that congenital ear defects are much more common on the right side and also familial. A fair percentage of people have small extra auricles.

The otologist was interested, not so much in the actual deformity of the ear because that could be put right with plastic surgery or prosthesis, but in the presence or absence of hearing, and over 50 per cent. of the cases of congenital malformation of the ear had also labyrinthine malformation.

Dr Farquharson, referring to the treatment of the condition, said that cauterising the opening with the cautery was not satisfactory. There was a tendency to a recurrence of the condition. Diathermy, however, had given quite good results and was easy of application.

Mr Aird, in reply, said—There is no difference in the sex-incidence of ear-pit ; inheritance is not sex-linked. I was interested in Dr Ewart Martin's experience that artificially-produced ear-pits may closely resemble the congenital varieties. Recent observers have not noticed a preponderant incidence on the right side ; perhaps the earlier German authors drew for their experience on a population which included large affected families with a high right-sided incidence ; in any given family, one side seems to suffer predominantly. The associated deformities, sometimes complex, of middle and inner ear I am not competent to discuss. Dr Scott's estimate of the incidence of ear-pit must of course be higher than mine ; the otologist must meet in routine otoscopy numerous symptomless pits which do not reach the surgeon. The conformation of the auricle varies more perhaps from individual to individual than does any other organ in the human body, and when we consider the breadth of range that separates the transparent shell-like ornament that completes a maiden's beauty, from the mutilated protuberance which adds ruggedness to the profile of pugilist or rugby-football forward, we may well be surprised that departures from the normal are not commoner than they are.

TUBERCULOSIS IN SUTHERLAND

WITH SPECIAL REFERENCE TO SURGICAL TUBERCULOSIS *

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THE selection of the subject of tuberculosis by a general surgeon may seem somewhat surprising, but for many years it has been part of my duty to act as Consultant to the Local Authority, to be responsible for the routine diagnostic radiography and for the artificial pneumo-thorax clinics. As a native of the county of Sutherland the constant problems presented by tuberculosis have caused me much concern.

The county of Sutherland, because of its geographical features and the distribution of its sparse population, presents peculiar difficulties in its Health Services even compared with neighbouring areas. I wish in particular to emphasise this point for it is not readily appreciated outside the county. The population is approximately 15,000, mainly confined to the fertile strip of land along the eastern seaboard. Here there are no large centres, and on the northern and western coasts the people are even more thinly dispersed in crofting and fishing communities. The interior of the county is a vast stretch of mountain-ous moorland. Sutherland covers an area of 2028 square miles and there are 823 miles of roads. Thus a large proportion of the people live from 50 to 80 miles from hospitals on the East Coast. The climate on the east is dry with an average rainfall of 30 inches, and sunshine records are good. In the west the rainfall is 40 inches or higher, but all over the county the atmosphere is clear and clean and there is an almost total absence of fog.

Over the ten-year period 1936-1945, 136 fresh cases of non-pulmonary tuberculosis and 162 of pulmonary tuberculosis were notified to the Medical Officer of Health. Over the same period 212 cases of non-pulmonary tuberculosis were actually under treatment, and these are classified as follows, according to the disease for which they were first referred for surgical opinion (see Tables I and II).

DIAGNOSIS.—A grave responsibility rests with the isolated surgeon in the diagnosis of early tuberculosis, and the help of our colleagues in the cities is often most welcome. The early diagnosis of hip-joint disease, tuberculosis affecting the sacro-iliac synchondroses, and genito-urinary disease have in particular given much thought and anxiety.

In *July* 1944 a healthy girl aged seven years was running in a race when she suddenly fell for no apparent reason. She complained of pain in her left hip and thigh and was carried home. The pain subsided

rapidly, but her parents noticed a slight limp, which persisted. In *August* clinical examination showed no abnormality in the hip except a painless limp. X-ray examination revealed nothing abnormal. Complete rest was advised for one month. *September.* Limp still present; slight limitation of internal rotation of hip. X-ray showed a relative slight decalcification above the acetabulum which might well have been a post-traumatic change, but it was felt that the condition was tuberculosis. Accordingly the case was notified and the child was transferred to an orthopædic unit where she remained under close observation for seven months. Repeated examinations did not substantiate the diagnosis, and eventually she returned to our hospital, still avoiding weight-bearing. In *July* 1945, one year after the onset of symptoms, a cold abscess appeared in the thigh. Subsequent

TABLE I

Classification of Types Treated

Empyema	. . . 4		Cervical Adenitis	. .	76
Ribs	. . . 8		Abdominal	. .	54
Shoulder	. . . 2		Genito-urinary	. .	7
Elbow	. . . 1		Others	. . .	11
Spine	. . . 16				—
Hip	. . . 11				148
Knee	. . . 7				
Ankle	. . . 7				
Dactylitis	. . . 3				
Bones (Miscellaneous)	. 5				
	—				
	64				

TABLE II

Age Distribution of Cases

-5	5-10	10-15	15-25	25-35	35-45	45-65	65-
22	33	42	41	46	13	13	2

X-rays showed a caries of the acetabulum with spread to the ilium. This case shows most clearly how difficult diagnosis may be even under the best conditions, and it is easy to imagine the disastrous deformity which would have followed had she been walking at home. Hospital beds should always be available for suspicious cases of bone and joint disease.

TREATMENT.—Conditions of appointment of the Highlands and Islands Surgeon make possible satisfactory co-operation with the Medical Officer of Health in the county. There is a free interchange of patients between Local Authority and Voluntary Hospitals. Although facilities for the treatment of surgical tuberculosis have been and remain obviously inadequate, an effort has been made both to treat and maintain contact with such patients. More might have been accomplished had it not been for the heavy demands of six years of war work.

During the years 1936-1945, 367 patients suffering from surgical tuberculosis were referred for consultation at the Lawson Memorial Hospital, Golspie. In addition 589 consultations were given at the Local Authority Hospital, and 183 at the homes of patients. The following table gives the results of treatment over a ten-year period :—

TABLE III

	Totals.	Satisfactory.	Improved.	Still Requiring Prolonged Treatment.	Died.
Skull	2	...	1	1	...
Empyema	4	2	...	1	1
Ribs	2	2	...	...	...
Costo-chondral . . .	6	...	3	3	...
Shoulder	2	2	...	...	...
Elbow	1	...	...	1	...
Spine	16	6	5	3	2
Hip	11	8	2	1	...
Knee	7	4	2	1	...
Tibia	4	3	...	1	...
Ankle	7	4	...	3	...
Dactylitis	3	3	...	...	...
Cervical Adenitis . .	76	37	22	17	...
Abdominal	54	34	9	10	1
Genito-urinary . . .	7	2	1	3	1
Bursitis	1	1	...	...	...
Lupus	1	...	...	...	1
Meningitis	8	...	...	...	8
	212	108	45	45	14

In making this classification those listed as "satisfactory" are in good health, and according to age group are able to attend school or follow their ordinary occupation. "Improved" are those who still require to be under observation, and whose health and working capacity are impaired, although the disease is quiescent. This group, together with the number who still require prolonged treatment, makes a total of 90 cases remaining under supervision.

Eight of the deaths were due to meningitis in which melancholy disease no treatment avails. All but one occurred in very young children. One patient died after operation for the relief of acute intestinal obstruction, and five of generalised tuberculosis.

The average death rate from non-pulmonary tuberculosis for the five-year period ended 1945 was 0·146, comparing favourably with the figure for Scotland as a whole for 1945 of 0·190.

PULMONARY TUBERCULOSIS

Cases of "idiopathic" pleurisy were numerous and have been regarded with suspicion especially when an effusion was present. Only four cases became infected : two recovered after repeated aspiration, one was referred to a chest unit for thoracoplasty, and one died. A large number of cases of pulmonary tuberculosis have been

treated by artificial pneumothorax. I have learned that the rapidly spreading type of unilateral disease in the young adult is indeed a surgical emergency, whilst the control of severe hæmorrhage by pneumothorax compares in urgency with the treatment of abdominal catastrophies.

This work has been done in the closest association with the Medical Officer of Health, and we have not hesitated to ask for expert guidance from our colleagues in the South in the many cases which are so difficult to assess.

PHTHISIS DEATH RATE.—As shown by the following table the death rate from phthisis in Sutherland has declined steadily over a number of years :—

Average death rate over 10-year period ended 1914 . . . . 1·351
      „   „   „   „   „   „   1925 . . . . 1·246
      „   „   „   „   „   „   1935 . . . . 0·913
      „   „   „   „   „   „   1945 . . . . 0·529

Note.—Death-rate from Phthisis in Scotland as a whole in 1945, 0·60.

Even although the incidence of all forms of tuberculosis in Sutherland remains high, the fall in the death rate shows that the resistance of the community is increasing; it also suggests that in difficult circumstances such treatment as was possible has not been unavailing.

COSTO-CHONDRAL TUBERCULOSIS.—Six cases of costo-chondral tuberculosis were treated over this ten-year period. Four were in the age group 25 to 35, and two in the age group 45 to 65. This condition is notoriously difficult to treat, and it may be of interest to give a brief description of the clinical types encountered. In all 6 cases tuberculosis of the vertebræ was excluded, and tubercle bacilli were demonstrated in pus from the lesions.

CASE 1.—Male aged 20 was first seen in 1924 suffering from a tuberculous abscess in the distal end of the radius. He made a good recovery after operation, but in 1932 was again admitted suffering from osteomyelitis of the femur. Operation was followed by satisfactory healing. In 1937 a cold abscess appeared over the sternum. At operation the costochondral junctions were diseased and were widely excised. After prolonged treatment by heliotherapy and ultraviolet exposures the lesion has remained healed for 4½ years.

CASE 2.—Male aged 28 years. Pleurisy with effusion in 1933. In 1934 a cold abscess appeared over the lower sternum and was allowed to burst. Treatment was refused until 1936 when operation was undertaken followed by ultraviolet exposures. The wound remained healed for two years, but recently abscesses have recurred and more cartilages are becoming involved.

CASE 3.—Female aged 26 years. A slight injury followed six months later by an abscess which was allowed to burst. Operation and Light Therapy. Healed for two years. No systemic infection.

CASE 4.—Male aged 27. Slight injury followed one year after by fluctuant swelling over lower costal cartileges. Treated by complete rest, repeated aspiration, and Light Therapy. After seven months the lesion appears quiescent and health is excellent.

CASES 5 and 6 are in age group 45-65. Both are in very fair health, but have recurring abscesses and multiple sinuses which resist all forms of treatment. One suffered from pleurisy six months before the manifestation of rib infection.

Undoubtedly when conditions are favourable as in case 4 treatment should be conservative, but here we are up against the ever-present difficulty of persuading an otherwise apparently healthy patient to submit to a prolonged period of rest.

Cases of bone and joint tuberculosis have been treated by the generally accepted routine conservative measures : rest, sunlight and reasonable immobilisation. Lack of suitable accommodation has proved a great handicap, and in addition several women have had to return home before treatment was nearly complete simply because there was no one left to supervise the household. The fortitude of these women and their strict adherence to instructions was truly remarkable.

A gamekeeper aged 35 was referred to me in 1934 suffering from spinal caries and lumbar abscess. After operation and prolonged fixation he was allowed home in 1938 with instructions to remain lying in his plaster shell. Some months later he was brought over seventy miles by ambulance for routine examination. He seemed unduly anxious until told that the result of X-ray examination was satisfactory. He then asked if he could see me alone, when he told me this story. While lying in bed one day he saw a fine specimen of a wild cat enter his garden. This was too much ! Taking advantage of his wife's absence from the house he managed to get out of bed, get his gun, creep to the window and shoot the marauder. Forgetful of everything else he went out, collected the cat and was discovered by his wife sitting on his plaster skinning the corpse. I am glad to say that his recovery was so complete that he is now waging war on the wild cat and fox on the wide open hill which he loves so much.

CERVICAL ADENITIS.—Of the 76 cases treated 65 were in children under the age of 15 years. This does not by any means represent the numbers in the county, for many parents pay little attention to enlarged glands. In fact if an abscess " bursts " and discharges freely it is often regarded as a satisfactory event. Parents are especially prone to regard the more chronic types of lymph-node tuberculosis with equanimity, but the acute exudative type naturally causes alarm. Twenty-three cases showed acute swelling and œdema followed by rapid caseation and abscess, indicating a massive dose of infection.

The removal of diseased tonsils was beneficial, especially where the submaxillary gland mass was involved. Over 90 per cent. of children suffering from cervical adenitis were found to have infected teeth and gums. It seems reasonable to suppose that constant and prolonged infection from the teeth may lower the resistance of the glands and render them more susceptible to the tubercle bacillus. A dentist of great experience has pointed out to me the danger of

unsuspected chronic infection from the first molar tooth which erupts at six years of age.

During the three years before the outbreak of war 44 cases of cervical adenitis living within easy reach of hospital were treated by conservative measures and ultraviolet therapy. Results were on the whole satisfactory. In-patient accommodation is woefully inadequate. Children requiring surgical treatment, repeated aspiration of abscesses which must be done at the optimum moment, solar and ultraviolet light therapy, etc., cannot in my opinion be treated satisfactorily as out-patients in a county like Sutherland where distances are so great.

ABDOMINAL TUBERCULOSIS.—Of the 54 cases referred for surgical opinion 39 required operation and 15 were treated conservatively. Of the 39 treated by operation 13 complained of persistent pain and tenderness in the right iliac fossa. In 10 the appendix was directly involved or kinked by a mass of enlarged ileo-cæcal glands. In 6 cases operation was necessary for the relief of acute intestinal obstruction, and in 10 for symptoms of sub-acute obstruction. In 7 cases the tubercular focus was found to be a pyosalpinx. Three cases of ascites in adults which continued to lose condition did well after laparotomy.

In many children suffering from recurring acute attacks of right-sided abdominal pain a simple lymphadenitis affecting the ileo-cæcal and ileo-colic glands was found, the glands appearing discrete, and without caseation or surrounding adhesions. The clinical picture was usually clear : acute onset of pain with high temperature, little or no nausea, a clean red tongue, and rapid subsidence of the symptoms in twenty-four to forty-eight hours. Even when the diagnosis from appendicitis could be made with reasonable certainty operation was usually advised, for I seldom had the courage to leave such a child at home twenty to eighty miles from hospital.

GENITO-URINARY TUBERCULOSIS.—In all cases the disease was already well established. One is in good health after nephrectomy four years ago, two are well healed following orchidectomy but both have since had pleural effusion, one case of epididymitis is improving with conservative treatment, and three suffered from generalised tuberculosis. The remaining case, a man aged 68, was first seen in consultation in August 1945, when he gave the following history : in June 1944 he had discomfort when sitting on hard surfaces, but otherwise had no symptoms until May 1945, when he commenced to have frequency and difficulty in micturition. For some weeks the symptoms had increased and there was now much pain in the perineum. Examination showed a tense, almost hard, extremely tender swelling in the perineum. The prostate was moderately enlarged, firm and nodular, and very tender. Pus aspirated showed scanty tubercle bacilli. To relieve the urgent symptoms it was necessary to evacuate the abscess by free incision. A small sinus remains, but apart from some frequency of micturition the patient is well and comfortable. This

instance of peri-urethral abseess following tuberculosis of the prostate perhaps warrants speeial mention.

It is appreeiated that in a country distriet the insidious onset of genito-urinary tuberculosis may easily be missed. It is well to send any suspicious ease to a hospital centre for complete investigation.

BURSITIS.—One ease only of tubercular bursitis was treated. This was in a girl of 16 whose father died of aeute phthisis and whose only brother suffered from adenitis. She had a huge, painless, but somewhat embarrassing cold abseess of the ischial bursa. This was treated by aspiration followed by complete exeision and primary closure. There has been no recurrence for four years.

PREVENTION AND CONTROL

The incidence of surgical tuberculosis in Sutherland has not fallen within recent years. Unhappily many young adults who had developed some immunity at home have eontracted tubereulosis under war conditions. Others may run the risk of infection on return to their homes. In the two World Wars the community suffered heavy casualties, so that the proportion of healthy adults in the eounty is small indeed. In my opinion the incidence of tuberculosis is likely to inerease unless steps be taken to protect the ehildren and young people by giving them better homes and a safe milk supply.

HOUSING.—It is not generally realised that the housing problem in a county sueh as Sutherland is really urgent. The oceasional visitor sees only the apparently solid stone-built cottage standing in beautiful surroundings and does not realise the truth.

Out of 136 eonsecutive notifications of non-pulmonary tuberculosis 57 per cent. were from crofters' houses, 25 per cent. from fishing villages, 17 per cent. from farm servants working on the larger farms, and 15 per eent. unclassified.

Owing to the peculiar system of land, tenure under the Crofter's Aet, the house is the property of the crofter and passes down the family. The houses are generally very old, and although stone built they are of poor construction. The inside walls are not damp proof, as the plaster is set direetly on the stone ; there is no damp proof course through the walls above ground level. Roofs are now generally slated but under the slates there is no felting overlay on the wooden sarking. The kitchen is used as a general living-room and as the fire is seldom out the walls are fairly dry, but in the room " ben the hoose," which is seldom used, the atmosphere is dank and cold and the walls are sodden with damp. The upstairs rooms are of poor construction and are wood lined. The ceilings are sloping and low and one cannot stand upright except in the centre of the room. The doors are so low that the unwary medical man frequently enters in a mildly stunned condition.

There is often a bed on the dark and ill-ventilated landing which is also used for stores.

Apart from generally poor construction many houses are in bad stances facing north, or as the people describe it " at the back of the sun." No sunshine reaches them for at least three or four months of the year. These dwellings are a silent reproach to the days of the clearances in the beginning of the nineteenth century.

LIGHTING AND VENTILATION.—Lighting of the whole house is inadequate. The kitchen and sitting-room have one window only. Upstairs lighting is usually from small skylights, although several houses have " storm " windows. At the back of the house there is only one tiny window which in the great majority of cases is incapable of opening. This window serves a small closet off the kitchen which is used by the grandmother or grandfather of the household or by anyone who is ill.

WATER SUPPLY AND SANITATION.—In the average crofter's house there is no water supply and only the most primitive sanitary arrangements. Every drop of water has to be carried in pails, often over very rough ground, in fair weather and in foul.

RECONDITIONING OF HOUSES.—The Housing Rural Workers' Acts of 1926 and 1938 empowered County Councils to assist in reconditioning houses. This was not adopted in Sutherland until the year 1930 and the measure was suspended at the outbreak of war. The Act had the considerable disadvantage of curtailing the completed value of the house to £400. In all, some 250 crofters' houses have been reconditioned at a total cost of over £24,000, the grant being a lump sum of £100 in respect of each dwelling. With the resources available this was a considerable achievement, but falls far short of what is required. Many houses are not fit for reconditioning. In 1938 seventy-four applications for grants were received in Sutherland ; of these rural houses thirty-seven, or 50 per cent., were classified as unfit for habitation.

In the fishing villages, although a small number of modern houses have been erected, there remain whole streets of dwellings in bad condition. These houses are extremely old and their construction is even worse than the average crofter's cottage, while too often the surroundings can only be described as squalid. Farm servants' houses are in a deplorable condition. Only a handful of new cottages have been erected.

It is clear, therefore, that housing in Sutherland is far from satisfactory. There has been little improvement during the past fifty years, and no doubt the conditions have a profound and intimate bearing on the prevalence of tubercular disease in its different forms, as well as on the general health of the people.

ACCESS TO HOUSES.—Before the problem of rehousing can be tackled on anything like the scale required, transport and access will have to be improved. Many of the crofts can only be reached by rough tracks over which even a horse and cart have difficulty in making their way. The hill shepherds are in even worse plight for they live

in inaccessible places only to be reached on foot. I stress this question of access to houses not only because of its importance in any future housing scheme but because of its direct bearing on the well-being of the families concerned.

MILK SUPPLY.—In the county of Sutherland the milk supply has been entirely unsatisfactory. There are three attested herds (about 150 animals) in Sutherland. Of these, only one supplies tuberculin-tested milk; in the other two, while the animals are attested, the premises are below the necessary standard. In other registered dairies (approximately 300 cows) the number of veterinary inspections is obviously inadequate, and in " exempted premises," where the average number of cows is 400, there is no supervision whatsoever. Thus the children at the larger schools in the county who are provided with milk from these sources are not protected from infection. The Medical Officer of Health has repeatedly urged that all milk supplied to schools should either be supplied from attested herds, or pasteurised, but his advice has not been taken.

The crofters have their own cows and none of these are attested. There have been countless instances of infection in children from these animals. A boy aged 9 years was referred suffering from cervical adenitis. His mother stated that the child had been ailing for some months. The neighbours had a very fine cow and the boy had been encouraged to drink as much milk as possible in order to build him up. " Unfortunately," she continued, " the cow has died, and I am so worried because we can't get good milk now." The Veterinary Surgeon informed me that this cow had died of acute tuberculosis. Subsequently two other members of the family developed adenitis and pleurisy.

The Department of Agriculture has for many years assisted crofters to improve their class of cattle by supplying service bulls on easy terms, but these have not been of milk-producing breeds but mainly Aberdeen-Angus or Shorthorn beef-producing animals. Cows are mated to. calve in the spring when best prices are available. This means that during the winter months when milk is most required production is at its lowest. Indeed it would be interesting to know how much condensed milk is consumed in crofting districts during the year. Arable land is scarce for growing winter food, and this is the crofters' greatest problem.

Efforts are being made by the North of Scotland Milk Marketing Board to improve the milk supply in the north and west of Sutherland, but this means that milk has to be transported in bottles some forty to fifty miles by mail car. To ensure a reasonably safe milk supply may only be possible by provision of small central dairy farms of good standard in the outlying crofting areas.

The buildings in which cows are housed are usually old and decrepit. Often the byre is an ancient building which was the dwelling-house hundreds of years ago. The average byre is a truly shocking place.

The floors are of rough paving or cobble-stones, very few of cement concrete, impervious to liquid. The inside walls are rough stone, and the divisions between animals are of undressed wood. No attempt can be made to provide sufficient floor or cubic air space, and lighting is usually non-existent. Even where some improvement has been made in buildings, the byre cannot possibly be properly cleaned for there is no water supply.

It stands to reason that under these deplorable conditions tubercle bacilli may live for years and healthy cattle become infected with ease. It is true that cows live outside for a considerable part of the year, but they are brought in for milking and for the winter months. Calves are born in surroundings which could hardly be worse.

Milk is stored under bad conditions; it cannot be easily cooled and is readily contaminated. Butter and crowdy (made from milk curd) is made in almost all crofts, and these valuable foods are also open to contamination.

The womenfolk in the crofts are showing the strain of the past six years, when they have not only looked after house, old folks and children, but have tackled the work of the croft as well. It seems intolerable that they should have to continue their incessant labour under such handicaps. It is truly amazing how such women continue to keep their houses spotlessly clean, and they surely deserve all the assistance possible to improve living and working conditions.

It is to the unsafe milk supply that we must attribute the fact that there is no diminution in the incidence of surgical tuberculosis in Sutherland. In the fishing villages there is much inter-marriage, and few families are free from a history of tuberculosis. All over the county are many young children who show intolerance and susceptibility to infection, and it cannot be doubted that milk often supplies a concentrated dose of tubercle bacilli. Recent researches in this country and in Sweden have proved that pulmonary tuberculosis is frequently due to bovine infection. The proportion in Orkney was actually over 25 per cent., and Sutherland may well equal these figures.

DIETARY.—There is a serious lack of vegetables in the diet in all parts of the county, and the Department of Agriculture could do much to stimulate an interest in horticulture.

Thus, widespread improvement in housing, a vastly safer milk supply, adequate transport and access and more healthy dietary are, in my opinion, essential steps to be taken to prevent the further spread of tuberculosis. The urgency of the problem is surely obvious.

MANAGEMENT OF POTENTIAL CASES OF TUBERCULOSIS IN CHILDREN.—As already indicated in Table III there are now some 90 cases of surgical tuberculosis requiring constant supervision and this does not by any means represent the total. It is unfortunately not uncommon in some parts of Sutherland to see little children, obviously not in robust health, burdened with heavy clothes, their

boots seeming too big for their thin legs, trudging home from school. Eventually they go to bed at an absurdly late hour in an ill-ventilated room. These children exist under conditions typically predisposing to tuberculosis and often show the premonitory symptoms of systemic infection ; they constitute the real problem of the immediate future. Given timely and sufficiently prolonged institutional treatment they can with certainty be cured.

It is clear that pulmonary tuberculosis and the difficult orthopædic cases should be treated in special units of the Central Institution, but in the Scottish Hospitals' Survey the number of beds allocated to cases of tubercular cervical adenitis and peritonitis appear to me to be totally inadequate. For the numerous children suffering from early surgical tuberculosis there is, in fact, no provision at all.

From my knowledge of the Highlander I consider that parents of such children would be reluctant to have them treated at a far distant sanatorium. In most cases these children do not appear really ill, but from the parents' point of view merely " run down," and their fear and resentment of the label of tuberculosis is understandable. A " Sunshine Home " or " Holiday Home," call it what you will except a sanatorium, built on the simple open-air principle within the county would in my opinion be the best solution and would eventually pay a handsome dividend in restoring health. The children would have a chance of living under healthy conditions with properly controlled rest and activity. Much-needed dental treatment could be given under favourable conditions. I am aware that an objection to such a scheme is the difficulty of continuing education, but from experience in treating this type of case in a general hospital I consider that three to six months is usually sufficient. This, after all, only means a prolonged holiday. Accommodation must also be found for cases of pulmonary and surgical tuberculosis returning from the Central Sanatorium or Orthopædic Unit as they should not, under present circumstances, run the risk of fresh infection in their own homes.

The long hours of sunshine and the clear air are being wasted in the treatment of disease, and the rural areas have lagged far behind the cities. To quote the late Sir Robert Philip in an address to the Edinburgh Sanitary Society in 1911, speaking on the physiological application of open-air in treatment : " The world has yet far to go before it realises practically the tremendous significance of this mighty principle. Its half-hearted application in prevention and treatment remains one of the most unintelligible sins of our age." Surely the ideals of this principle could nowhere be more easily attained than in a county such as Sutherland.

The views expressed in this paper are personal, but I wish to acknowledge the ready assistance of Dr K. A. MacRae, Medical Officer of Health, and of the general practitioners in Sutherland.

My main object has been to draw attention to the fact that measures for the prevention and control of tuberculosis in this Highland county

are hopelessly inadequate, and indeed have progressed little for many years. The main reasons are :—

Firstly, that in a county where the rates are abnormally high, one penny in the pound producing approximately £200, the financial position has been very difficult. In ordinary times also, many people find living precarious and there is much actual poverty.

Secondly, and most important, there has been a complete lack of understanding, often amounting to apathy and sometimes even obstruction, amongst the people generally. Recently there have been signs, especially amongst the womenfolk, that interest is slowly awakening.

I have confined my remarks to the county of Sutherland, but am aware that similar conditions prevail in many other parts of the Highlands. It is also true, however, that much has been done in some comparable rural districts both in this country and abroad to detect and eliminate bovine tuberculosis, and to improve housing. I do not doubt that a great deal can yet be accomplished throughout the whole Highlands and Islands area if the urgency of the problem is appreciated.

SOME MEMORIES OF THE OLD CITY HOSPITAL, AND OF DR CLAUDE BUCHANAN KER *

By C. C. EASTERBROOK, M.A., M.D., F.R.C.P.E.

To most of you of the present generation Claude Buchanan Ker is probably just a name ; but " C.B.K." was a dear friend of us both—and in his day " Claude " (as he was to his intimates) had many close friends, now, alas ! mostly passed on. So when, some time ago, Dr Joe asked me to present the prizes on this occasion, he suggested that I might give you some memories of Claude Ker, and also of the old City Hospital at the foot of Infirmary Street as I knew it, more than fifty years ago—and about ten years before its replacement in 1903 by this fine hospital at Colinton Mains in the southern suburbs of the city.

To those of you who are interested historically in the Edinburgh Medical School and Hospitals I would remind you that the old Royal Infirmary of Edinburgh, before its replacement in 1879 by the present Royal Infirmary between Lauriston Place and the Meadows, was situated for about 150 years close to the old University in South Bridge. Its main or south front faced Drummond Street, but it was entered from Infirmary Street ; and it comprised two main sections : (1) The Medical Hospital, entered about half-way down Infirmary Street on its south side ; after its replacement in 1879 by the Royal Infirmary Medical Wards facing the Meadows, it was demolished in 1884, and its site is now occupied by a Corporation School and Public Baths. (2) The Surgical Hospital, entered at the foot of Infirmary Street, and occupying the premises of the former Royal High School ; after its replacement in 1879 by the Royal Infirmary Surgical Wards next to Lauriston Place, it served as the City Fever Hospital from 1884 for about twenty years, that is, till its emigration in 1903 to Colinton Mains ; and it now houses the Commerce, Geography, and Natural Philosophy Departments of the University. The *original* " Fever Hospital " of the Corporation of Edinburgh, from 1870 to 1884, was the former Canongate Poorhouse at the foot of Tolbooth Wynd ; but it continued to serve as an emergency Fever Hospital between 1884 and 1903.

My first acquaintance with the old City Hospital at Infirmary Street was when, as a senior medical student about 1890-91, I entered my name for the Fever Cliniques, which were then optional, not compulsory. Dr Maxwell Williamson, Assistant M.O.H. for the City (who was acting temporarily for Dr A. F. Wood, Medical

* Address given at the Nurses' Prize-Giving at the City Hospital, Edinburgh, on 26th June 1946.

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Superintendent), enrolled me, and then remarked, " Have you ever seen smallpox ? " " No," said I. " Would you like to see some cases ? " said he. " Yes," said I. And thereupon he vaccinated me, and straightway took me down to the original " Fever Hospital " in the Canongate, where some 20 cases in various stages of the disease were isolated and being treated—not " a bonnie sicht," I can assure you. But it hardly needs me to tell you that my thorough vaccination just before the said visit ensured my protection. The Fever Cliniques, which I duly attended later at Infirmary Street, were given by Dr Claud Muirhead, Visiting and Consulting Physician from 1891 to 1896, who had recently retired from his appointment as one of the Physicians to the Royal Infirmary.

My next acquaintance with the old City Hospital was as House Physician from 6th January to 23rd April in 1894, one of several house appointments in Edinburgh hospitals during the two years following my medical graduation in 1892 (and the only salaried one). At the City Hospital in 1894 Dr Claud Muirhead was my respected and a charming " Chief," and my days there were very happy ones. Although exposed to all the ordinary infectious fevers, I enjoyed excellent health —not even a sore throat. At that time there was only one house physician ; and during my appointment, in addition to some 200 patients in residence on taking up duty, I admitted fully 500 others, there being distinct outbreaks of scarlatina and smallpox in the city, in addition to the usual run at that time of cases of enterica and diphtheria, erysipalas, etc. So I had plenty hard work—and in my experience plenty work and plenty play or recreation, both at all times within the limits of moderation, are the best recipe for health and happiness. At the " City " in 1894 the resident staff formed a " happy family," and I think that this united feeling was fostered to some extent by an idea of isolation from the outside community, owing to the nature of the work of the Hospital—an idea which, I understand, seemed more real later at Colinton Mains, but for wholly different, and geographical, reasons ! Here, then, in spring 1894 were gathered a happy band of workers. *Firstly*, Dr Andrew Fleming Wood, Medical Superintendent, affectionately referred to as " Daddy Wood," although a confirmed bachelor ; capable administrator in the daily running of the Hospital, and expert in the diagnosis of the various fevers ; a genuine Scot, quiet and humorous, genial and sociable, kindly and accessible, and much esteemed and beloved by the staff. In the evenings after the day's work he enjoyed a chat over a pipe and glass of toddy. *Secondly*, Miss Edith Sandford, Matron, the soul of efficiency at her work, keen, energetic, and progressive, and strict disciplinarian, retaining at the same time the loyal devotion and warm affection of her staff. At her request I gave a course of lectures on Fevers to the nursing staff, the first course of its kind to the nurses in the history of the Hospital ; these lectures were given at 7.30 a.m. as being the most suitable hour for both the day

and the night staffs. And *Thirdly*, the nurses themselves, who, of course, formed the main personnel of the " happy family." In my time they were a bright and cheery lot on the whole. They still included a very small and last remnant of the Old School, worthy and devoted women, self-taught and self-trained in the school of their own experience. But the great majority were Moderns—both the Seniors, who held the more responsible posts in charge of wards, fine women, devoted to their profession ; and the Juniors, in course of training, also keen on their work, and including the usual sprinkling of lively and sparkling elements.

After spring 1894, during the ensuing summer, autumn, and winter terms, I was followed in succession by other three house physicians ; and after the expiry of our respective periods of office, the four of us, and also Dr Claude Ker, who had been a house physician in 1892, from time to time used to forgather at the Hospital of an evening and to enjoy Dr Wood's genial hospitality, discussing all the topics of the day and hour, including the Hospital gossip, and telling many yarns and the like. In this way arose " The Fever Board," as we called ourselves, the first photograph of which, taken in 1895, shows the six of us grouped in front of an old doorway in High School Yards, with the year " 1697 " boldly engraved above on its triangular stone pediment. These social meetings of " The Fever Board " in the winter months continued during Dr Wood's remaining days until his death in March 1896 and during the earlier years of his successor, Dr Claude Ker ; and " The Fever Board " gradually increased in number, its last photograph, taken in 1899 before the same old doorway, showing a group of fourteen former house physicians of the " City."

And now to tell you more particularly of Dr Claude Ker himself, and about the origin of his Memorial Medal. Claude Buchanan Ker was born on 22nd March 1867 at Cheltenham, and he was named after his father Dr Claudius Buchanan Ker, a well-known general practitioner there. Young Claude was educated at Malvern College, where he eventually rose to be head boy of the School—early testimony not only of his intellectual ability but also of his character and personality generally. In 1886, at the age of nineteen, having decided to follow his father's profession, he started on his medical curriculum at Edinburgh University, where four years later, in 1890, he graduated M.B., C.M. During the ensuing two years he held a succession of house appointments : in winter 1890-91, as clinical assistant at the Royal Edinburgh Asylum, where he gained the Medico-Psychological Association Certificate for Proficiency in Mental Diseases ; in summer 1891, as house surgeon at the Royal Infirmary ; in May, June and July 1892, as house surgeon at the Royal Maternity and Simpson Memorial Hospital ; and in autumn 1892, as house physician at the old City Hospital, where he became specially interested in the study of fevers. He then became assistant to the late Dr Thom of Crieff, where he first met his future wife. Returning in due course to

Edinburgh, he commenced a general practice on his own account at 4 Howard Place, Inverleith, but whilst so engaged he spent much of his time at the City Hospital continuing his special study of fevers.

In spring 1896, following Dr Wood's death on 4th March, he was appointed Medical Superintendent of the City Hospital at Infirmary Street ; and in August 1896 he became M.D. and was awarded a Gold Medal for his Thesis on " Enteric Fever." In 1901 he was elected F.R.C.P.E. The project of the new City Hospital at Colinton Mains was carried out during the regime of the late Sir Henry Littlejohn as M.O.H. for the City ; but its chief promoter was the late Bailie Pollard, Convener of the Public Health Committee of Edinburgh Town Council ; and he and Dr Ker naturally took a special interest and active part in the preparation of the plans. The new City Hospital was finally opened on 13th May 1903 by His Majesty King Edward VII. Here Dr Ker spent the rest of his busy life ; and it may be justly recorded of him that he laid the solid foundations of the Hospital's fame as one of the best—if not the best—of its kind in the country ; and at the same time he was its respected " Chief " and held in much affection by the staff. Meantime also he made his reputation as a leading authority and consultant in infectious diseases. In 1904 he was appointed University Lecturer on Infectious Fevers. His *Manual of Fevers*, published in 1909 and brought up to date in 1920, was long regarded as a standard work on the subject in this country and in America. As a teacher he was very popular, lucid, stimulating, and practical. In 1925, at the time of his death, he was President of the Fever Hospital Group of the Society of Medical Officers of Health.

Apart from his life-work as medical specialist and public official, Claude Ker had many other interests. As a boy at Malvern he was a member of the School Volunteer Corps and in command of an artillery battery ; when medical superintendent of the City Hospital, he received his commission in 1898 as Surgeon-Lieutenant in the Queen's Brigade of the Royal Scots ; later he became second-in-command of the Volunteer Medical Unit attached to the 4th Infantry Brigade ; in 1908 he was promoted Major R.A.M.C. (Territorial Defence) ; and during the 1914-1918 War he served for a time at North Queensferry, Redford and Stobs, but had to be released from military service owing to the urgent demands of his office at the City Hospital. He also had strong literary tastes, and retained during life his old school affection for the Classics, both Latin and Greek ; but he made a special study of the literature relating to Napoleon Bonaparte, of whom he was an enthusiastic admirer, as also a very interesting exponent of his career and campaigns. He was also much interested in athletics, and especially a keen follower of Rugby football ; and although unable himself, owing to an impairment of eyesight, to take part in such games, he was for a time an Honorary Vice-President of Edinburgh University Athletic Club. The foregoing bare facts of his life shows that its

guiding principles were hard work, and loyalty and devotion to the
service of his fellows. ·

. As a man Claude Buchanan Ker was very human and very social;
a man of wisdom, broad outlook, and sound judgment; a man of
much sympathy and humour; a man who took a kindly and always
tolerant view of his fellows and their foibles; a man who made many
friends, to whom he always remained loyal. Owing to his strong
social instincts he was one of the main moving spirits in the formation
of at least three social medical clubs in Edinburgh in his early post-
graduate days. I have already referred to " The Fever Board " at
the old City Hospital, which flourished from 1894 to 1899. " The
Edinburgh Royal Infirmary Residents' Club " was inaugurated in
spring 1895, with the late Dr Alexander James as President, C. B. Ker
as Secretary, and R. J. A. Berry as Treasurer; it still flourishes, with
its many members scattered throughout the world. In his Residency
days at the Royal Infirmary, and for years thereafter, no social gathering
of the Residents was complete without Claude Ker and his inimitable
recitation of the amusing verses of " The Hunkey Kid "—the story
of an amateur dramatic performance, in which a notorious wrestler
is called in at the last moment, owing to the illness of the original
performer, to take his place; but unfortunately " Charles the Wrestler,
imbued with poisonous benzine," is " lamentably drunk " when the
time arrives for his appearance on the stage, where he sees red, and
" hurls his opponent, and other players, into the orchestra," etc. This
recitation, which C.B.K. gave with vivid expression, always convulsed
the house with laughter. The third Club, formed in December 1899,
was called " The Heptagon," as it consisted originally of only seven
members—Andrew Balfour, Richard J. A. Berry, John Wheeler
Dowden, James Stewart Fowler, Claude B. Ker, Arthur Logan Turner,
and myself; of whom Berry and myself are now the only survivors.
We met in each other's rooms in turn, during the winter months
mostly, and it was up to the host for the evening to entertain the
party with some literary contribution on any subject except medicine,
" Shop " being strictly barred. " The Heptagon " was later called
" The Octagon," gradually included additional members, and
celebrated its 25th Anniversary with a dinner at the Scottish Con-
servative Club, Edinburgh, on 20th December 1924. At this dinner
I sat beside C.B.K. and we exchanged many memories of our happy
hospital days. Little did any of us foresee that we would lose him so
soon afterwards.

In appearance Claude Ker was of medium height, with brown
hair, fair reddish moustache and greenish hazel eyes, and he wore a
monocle in his right eye as the most handy means of correcting an
extreme degree of short-sightedness (with some strabismus), which
usually made him keep his eyes semi-closed when without the aid of
his monocle. His portrait in the Board Room at the City Hospital
(an enlargement from a snapshot without his monocle), does not do

him justice, making him to peer unduly and to look too serious, and lacking his humorous twinkle.

Our dear friend died on 4th March 1925, at the untimely age of fifty-eight, after twenty-nine years' service at the City Hospital, a victim to the zeal of his work and to influenzal pneumonia ; and his mortal remains were laid to rest on 7th March in Morningside Cemetery by his friends of " The Octagon " and his elder boy.   He was married on 1st August 1905 to Miss Katharine M. Thom, daughter of Dr Thom of Crieff, and at the time of his death he was survived by his widow and their young family of two sons and three daughters ; of whom the youngest child (also named Claude Buchanan) joined the Royal Navy in the 1939-1945 War, and very sadly lost his life at the age of eighteen through the torpedoing of his ship in the Malta convoy in August 1942.

Shortly after his death Claude Ker's many friends were anxious to raise a fund to perpetuate his memory ; and this took the form of his gravestone in Morningside Cemetery, and of his memorial plaque at the City Hospital, which was unveiled on 29th September 1926 ; and the residue of the fund was invested by trustees for the provision of the Claude Buchanan Ker Memorial Medal, which has been presented to-day, and will—it is hoped—be presented in future annually at the Nurses' Prize-giving.   For, as Shakespeare tells us, " a great man's memory may outlive his life."

NEW BOOKS

A Primer of Electrocardiography. By G. BURCH, M.D., F.A.C.P., and T. WINSOR. M.D. Pp. 215, with 235 figures. London: Henry Kimpton. 1945. Price 18s. net.

This book has been written to enable one who is unfamiliar with the subject to obtain a fundamental knowledge of electrocardiography in the most direct manner. The matter is presented in a clear, concise and dogmatic style which is possible since the more controversial issues have been omitted. There are large numbers of diagrammatic illustrations which should be exceedingly helpful, but it is rather a pity that the time marking is so prominent and the irregular form of the squared background distracts the eye from the main figure. The book is primarily intended for beginners and for them it should prove exceedingly useful.

The Extremities. By D. P. QUIRLING and Others. Pp. 117, with 107 illustrations. London: Henry Kimpton. 1945. Price 14s. net.

The scope of this book is so limited and the factual statements are so elementary that it is doubtful if it can be recommended to students of anatomy whatever final purpose they may have in view. The line drawings are clearly executed and produced but contain many inaccuracies as in the position of the patella on pp. 86, 87 and 88 and the insertion of the serratus anterior on p. 16. The real value of the book might have lain in the illustration of the motor points of muscles (despite the recognised variability) but though these are given for many muscles they have been omitted from muscles of such diagnostic importance as teres minor and abductor pollicis brevis.

Principles and Practices of Inhalational Therapy. By A. L. BARACH, M.D. Pp. xvi+315, with 59 illustrations. Oxford: Blackwell's Scientific Publications Ltd. 1945. Price 25s. net.

The importance of oxygen and other inhalational therapy is shown by their widespread use in many pulmonary and other diseases, but to ensure the greatest advantage from the method it is essential that the physician and his assistants possess a thorough knowledge of the indications for its use as well as of the technique to be employed. Dr Barach has supplied this information. After describing the history and the physiological background he describes the appropriate inhalation therapy for a large number of individual disorders, including such things as arteriosclerosis, hæmorrhage, migraine, head injuries and hiccough. Several chapters are devoted to a description of various kinds of apparatus and there is an interesting account of research into respiratory function.

The book will rank as a standard work on this important subject.

The Pocket Oxford German Dictionary. Compiled by M. L. BARKER and H. HOMEYER. Pp. xvi+432. Oxford University Press. 1946. Price 5s. net.

This little dictionary aims at presenting the German language in such a way as to reflect the current vocabulary of daily life. For its size it contains an amazing amount of information. This has been accomplished by judicious selection and by the omission of obvious compounds. The material is set out in a manner that should facilitate ready consultation without loss of time. A short synopsis of grammar has been included, and in the appendix are several useful tables, including one on German abbreviations. The book has been excellently produced and should serve a useful purpose.

Carbohydrate Metabolism. By S. SOSKIN and R. LEVINE. Pp. viii+315, with 42 tables and 75 figures. Chicago : University of Chicago Press. 1946. Price— not quoted.

Before one has read very far into this book it is realised that one is dealing with the work of authors who not only understand the minute details, but who can also record their views in the clearest fashion. The more abstruse points of the subject have been incorporated without disturbing the main flow of ideas, in a way which can only be described as brilliant. This result has been achieved partly by the use of numerous diagrams which are as original as they are helpful.

The book covers the biochemistry and physiology of carbohydrate metabolism, and then gives a most lucid account of the action of the related endocrines. It concludes with the various applications of this study to Clinical Medicine. The authors have achieved their aim of integrating the various viewpoints of the subject in the most excellent fashion. It is a volume which will find its way into the library of every biochemist, physiologist, and pathologist, for it has supplied a long-awaited want, and to the reviewer it has been the most stimulating book which has come his way for many years. There is also an extensive bibliography covering all the important papers published in this subject during the past thirty years.

It is to be hoped that as the subject develops in the next few years, the authors will be able to produce further editions. It would be a tragedy indeed if a text of this value were ever allowed to become out of date.

NEW EDITIONS

Bulletin of the Health Organisation—League of Nations. Volume XI, 1945. Pp. 235. Obtainable from Allen & Unwin Ltd. Price 6s.

Ten volumes of the Bulletin have so far appeared and it was considered desirable to publish a comprehensive index, but as this would give a rather incomplete picture of the work of the Organisation it has been decided to produce a complete bibliography covering not merely the Bulletin but other papers containing the technical work of the Organisation. This includes thousands of studies published by the Health Organisation and should serve as a useful guide to information on many aspects of Public Health work.

Practical Biochemistry. By A. T. CAMERON and F. D. WHITE. Fifth Edition. Pp. x+216, with 4 plates and 23 text figures. London : J. & A. Churchill Ltd. 1946. Price 12s. 6d.

The size of this book gives little indication of the amount of important elementary biochemistry which it contains. It covers all the simpler biochemical tests and most of the simpler analytical procedures.

The instructions are clear and should be easily followed by the intelligent student. The complete series of experiments described would require a longer course in Biochemistry than is usually given in British Universities, but as a text, it could still be used with advantage in shorter courses. It is a book which one could recommend confidently both to medical students and to their teachers.

Modern Anæsthetic Practice. Edited by Sir H. ROLLESTON and A. MONCRIEFF. Second Edition. Pp. viii+150, with 8 figures. London : Eyre and Spottiswoode Ltd. 1946. Price 12s. 6d.

This *Practitioner* handbook, first published in 1938, was reprinted in 1941. Since then many changes have occurred and the remarkable advances in anæsthetic practice during the war years have necessitated very considerable revision of the text. This small book gives an excellent account of current methods and should be of the greatest interest to the general practitioner as well as to the specialist.

A Pocket Surgery. By PHILIP H. MITCHINER, C.B., C.B.E., T.D., M.D., M.S., F.R.C.S., D.CH., D.L., and A. HEDLEY WHYTE, D.S.O., T.D., M.B., M.S., F.R.C.S. Second Edition. Pp. vii+272. London: J. & A. Churchill Ltd. 1946. Price 8s. 6d.

The second edition of this book will prove of value both to the surgeon returning from the Forces and to those who continue to care for the Forces in the various garrisons abroad and at home. The terse phrasing of the outstanding points of diagnosis and treatment makes this small book a concise *vade mecum* embodying the essentials of the various surgical injuries and diseases which are likely to be met in civilian and military surgery.

An Introduction to Biochemistry. By W. R. FEARON. Third Edition. Pp. x+569. London: William Heinemann (Medical Books) Ltd. 1946. Price 21s. net.

The third edition of Professor Fearon's book is a thoroughly revised and well up-to-date text-book of General Biochemistry which will meet all the requirements of the advanced student. It will also find many uses for those who require a good, sound reference book on the subject, for it is full of readily accessible information, and should be especially useful to medical men who care to refer to the fundamentals of Clinical Chemistry.

The book has been expanded in this edition by several new sections on recent biochemical advances, and there is also added a new chapter on Tissue Chemistry which, if not equal in excellence to the others, at least makes a start on the discussion of a very complex topic. The text is profusely illustrated with formulæ, equations, diagrams, and tables which considerably enhance its value as a book of reference.

The Physiological Basis of Medical Practice. By C. H. BEST, C.B.E., F.R.S., and N. B. TAYLOR, M.D., F.R.C.S.E. Fourth Edition. Pp. xiv+1169, with 497 illustrations. London: Baillière, Tindall & Cox. 1946. Price 55s.

This new edition of this well-known work has undergone considerable change, and now appears in two-column format which should make for easier reading and handling. The book has been written to act as a link between the scientific work of the laboratory and clinical practice, thus serving to promote continuity of the physiological point of view throughout the whole undergraduate curriculum. Special emphasis has been laid on clinical physiology and on the results of clinical research.

This excellent work, the product of the Toronto school, can be thoroughly recommended to all who are interested in the clinical application of physiology.

BOOKS RECEIVED

BAILEY, CHARLES PHILAMORE, M.D., Edited by. Diagnosis and Management of the Thoracic Patient . . (*J. B. Lippincott Company, London*)	24s.
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THE SPREAD OF INFECTIVE HEPATITIS AND POLIOMYELITIS IN EGYPT *

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Historical.—Epidemic or catarrhal jaundice, once named the jaundice of campaigns, has long been appreciated as an illness common to soldiers engaged on military operations. Cases occurred during the South African War, the Great War and the recent world conflict. The disease is world wide in distribution, but the Mediterranean littoral has always been one of high endemicity. From October to November of 1915, some 25 per cent. of a section of British troops serving in Gallipoli and Alexandria were affected (Martin, 1917).

Determined efforts to discover the mode of transmission of infective hepatitis have been unrewarded. Willcox (1916) studied the condition at the time of the Gallipoli campaign and concluded that the disease started as a gastrointestinal infection (see also Martin, 1917). Simultaneously army bacteriologists performed investigations on blood, urine and liver biopsy tissue of patients, but could recover no specific cultivable bacterium (Hunter, 1922). A good account of the poor sanitary conditions then prevalent in the military sphere is contained in a leading article in the *Lancet* (1945). The researches of Kartulis (1916) of Alexandria were also negative, and he presumed that the causal organism of infective hepatitis was invisible, like that of yellow fever. Continuing, Kartulis (1916) declared at a medical conference in Egypt that the pathogenic agent was intimately related to sewers and sea water because the annual case incidence had progressively decreased from 1898 to 1916 consequent upon the introduction of modern sanitary drainage to Alexandria.

From 1940 to 1943 infective hepatitis returned as a major cause of sickness among British troops in Crete, Syria, Palestine, Egypt, Libya, Cyrenaica, Malta, North Africa, Sicily and Italy (see Richmond and Gear, 1945). Simultaneously, three associated varieties of jaundice drew attention for the first time in large numbers, namely, homologous serum jaundice following blood transfusion, post-arsenical jaundice after treatment for syphilis, and jaundice after inoculation with contaminated batches of yellow fever vaccine. The present paper has been written for the interest of Service Medical Officers who have

experience of living conditions in Egypt and are acquainted with the epidemiological behaviour of infective hepatitis.

ÆTIOLOGY OF INFECTIVE HEPATITIS

van Rooyen and Gordon (1942) tried, unsuccessfully, to infect mice, guinea-pigs, rabbits, a pig, jerboas, gerbilles, monkeys and baboons with material from cases of infective hepatitis. Blood, serum, stomach washings and bile were introduced by the subcutaneous, intraperitoneal, intracerebral, oral and rectal routes, but without effect. More recently one of us fed by stomach tube two *Cercopithecus griscoviridis* monkeys with 20 gms. of dried infective hepatitis plasma, emulsified in 100 c.c. of saline mixed with 2 gms. of powdered glass, but in vain. No bacterium could be blamed, and it was assumed that the disease was due to a filterable virus. Cameron (1943), who studied the natural disease in Palestine, arrived at the same conclusion. Likewise, negative animal experiments were conducted on homologous serum jaundice in West Africa by Findlay and Martin (1943), in England by MacCallum and Bauer (1944), and in the United States by Oliphant, Gilliam and Larsen (1943) and others.

A number of investigators, notably Cameron (1943), diverted their energies to human transmission tests, and Cameron successfully reproduced infective hepatitis in six volunteers injected intramuscularly with 1 or 2 c.c. whole blood or serum obtained from cases of jaundice in the pyrexial and apyrexial phases. One of these men developed jaundice after thirty days and within the next five months the remainder did so. Similar results were recorded by others, both with material obtained from natural epidemic jaundice and serum jaundice (see MacCallum, 1944). The findings in general resembled observations on post-yellow fever vaccine jaundice.

The question of whether infective hepatitis could be transmitted to man by other routes, and by pathological material apart from blood or serum has also been examined and the first answer probably came from Germany, but the evidence was unconvincing. Thus Voegt (1942) mentioned that the oral administration of duodenal content to four volunteers induced it in one person. Suggestive examples of infection were recorded in two German women, one of whom drank a large volume of urine and the other swallowed a quantity of hemolyzed erythrocytes. Feeding experiments were performed in West Africa by Findlay and Martin (1943), who state they reproduced post-yellow fever vaccine jaundice in human volunteers by oral administration of nasopharyngeal washings after an incubation period of twenty-eight to fifty days.

INFECTIVITY OF FÆCES

The dissemination of infective hepatitis in the Western Desert was studied by Kirk (1945) of the Second New Zealand Expeditionary Force, who observed the progress of an epidemic from August 1942

to January 1943 among two groups of men who fought at the battle of El Alamein.

From August 1942 to January 1943 the New Zealand Division in the Western Desert produced 2095 cases of hepatitis. During September and October 1942 there were 1137 cases, and it was found that of these, 1059 cases occurred among 7500 men in the Alamein Line and 78 cases among 3900 in rear areas (within five to ten miles of Alamein). This concentrated attention on the site, as the front line troops occupied an area about five miles square and all units who spent thirty-five to forty days there before the start of the epidemic were involved. Units withdrawn after a shorter stay than the remainder were less affected. After the front line troops left this area the epidemic commenced to subside.

Other troops in the Alamein line were not concerned at this time, so if the site were to be incriminated it had to be different from the rest of the front line at Alamein.

Common factors to all at Alamein were food, water, living conditions, heat and fatigue, so these could not account for the localised epidemic among New Zealand troops. New Zealand troops had never exhibited any undue susceptibility to the malady. The possibility of an unknown vector was ruled out. Spread by droplet infection was unlikely in the front line units as they were living in dispersed formation with little close contact and no tents or messes. On the contrary, the fit troops in rear areas were living in a more congested state and although the incidence of catarrhal infections was low, opportunities for droplet spread were numerous.

The third possibility, and the one of choice, was that the disease was fly borne. Flies were present in millions everywhere at Alamein, both front and rear, and as the site seemed to be responsible it was thought that in the forward area the insects were infected locally. The New Zealand ground was one of the few parts recently captured from the enemy. It was filthy with excreta and imperfectly buried German and Italian corpses, and it was learned from patrols and prisoners that the enemy themselves were experiencing an outbreak of hepatitis. Thus the epidemic was attributed to local contamination of flies arising from the faeces and cadavers strewn over the battlefield, where food, hands and mess tins could not efficiently be protected. In support of the above, Kirk (1945) commented that infective hepatitis did not spread in General Hospitals, Base Camps or P.O.W. cages, where sanitation was good and fly control satisfactory. Richmond and Gear (1945) stated that after the retreat from Gazala to El Alamein the fly menace assumed the proportions of a plague.

The Consulting Physician, Brigadier Sydney Smith, who examined many patients from the Western Desert, maintained that the horse fly was another possible vector which should be placed under suspicion. Likewise, Colonel J. S. K. Boyd, D.D.P., G.H.Q., M.E.F., repeatedly expressed the conviction that the disease might be disseminated by faeces and that examination of alimentary mucosa for evidence of

virus inclusion bodies though technically a difficult operation, might provide information.

Human Experiments.—Owing to the military importance of obtaining accurate information as to whether the agent of infective hepatitis was transmitted by stools and urine, it was proposed to perform human feeding experiments. An official request was made through British channels for authority to conduct human volunteer experiments in the M.E.F., and the proposals were accompanied by a detailed experiment designed by one of us (C. E. v. R.) for testing the possible infectivity of stools and urine, and the scheme was submitted to the Medical Research Council Jaundice Committee in August 1943 for approval. Unfortunately, permission to employ human subjects was refused.

Working independently, Dr John Paul of Yale University and other members of the United States Commission on Neurotropic Virus Diseases were studying the problem of infective hepatitis in the Mediterranean theatre of war, with particular reference to its mode of spread. Stools were collected from infected U.S. troops located in the Middle East, frozen with carbon dioxide and transported by air to America where human volunteers were fed with fæcal material, and the condition was reproduced at a site many thousands of miles distant. The results are summarised in two publications by Havens *et al* (1945) and Paul, Havens, Sabin and Philip (1945) in the following quotation : " When fæcal material from patients with the naturally occurring disease was fed to human volunteers, two out of three contracted the disease in 20 and 22 days respectively. Serum obtained from these two patients in the pre-icteric phase was filtered (Chamberland 2) and immediately afterwards heated (56° C. for 30 minutes). This heated serum filtrate (MK) produced infectious hepatitis when fed to four out of five volunteers with an incubation period ranging from 23 to 34 days. The same material was simultaneously inoculated parenterally in the same amount and produced infectious hepatitis in six out of eleven volunteers with an incubation period ranging from 20 to 31 days. Some of the latter group of volunteers had recovered some months before from serum jaundice, but it did not protect them against an attack of infectious hepatitis."

Thus employing one strain of infective hepatitis virus, jaundice was produced in six out of eleven subjects when serum was inoculated, four out of five volunteers when serum was fed ; and in two out of three subjects when fæces were fed, and the incubation period was invariably less than thirty-four days in these experiments.

A separate claim to have demonstrated the virus of infective hepatitis in human fæces has been lodged by MacCallum and Bradley (1944), who fed rheumatoid arthritic patients with fæces from early cases of jaundice and so reproduced the disease, after an incubation period of twenty-seven to thirty-one days.

These two accounts, American and British, indicate that the virus may be primarily viscerotrophic in affinity for gut tissue, and second-

arily, invasive for liver ; also the incubation period of the experimental disease induced by alimentation was shorter than that produced by parenteral inoculation.

Additional evidence of the infectivity of human fæces has been supplied from West Africa by Findlay and Willcox (1945), and from America by Neefe, Stokes and Gellis (1945), and to-day there is sufficient proof that the virus of infective hepatitis is both present in fæces and possesses adequate powers of viability to enable it to be transmitted by excreta.

EPIDEMIOLOGY AND SPREAD

The mode of transmission of the disease has puzzled many workers. Spooner (1943) scrutinised the case histories, movements, and contacts of numerous patients in Egypt during 1942, but without luck. Since the ætiological agent has been discovered in fæces, one is tempted to recapitulate the course of epidemiological events in retrospect.
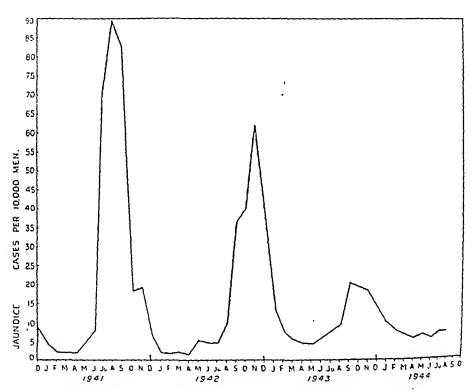
Seasonal Incidence.—Through the courtesy of Colonel N. Hamilton Fairley and Lieutenant J. B. Fletcher, Officer Commanding Statistical Subsection Medical History and Information Section, it was possible to estimate the number of cases which occurred among the Australian forces who served in Egypt and Libya throughout the year 1941. During the period up to September 1944 some 25,827 cases were notified in United Kingdom, Dominion and Colonial troops serving in Egypt, Cyrenaica, Tripolitania, Palestine, Syria, Cyprus, Sudan, Eritrea, Malta and Aden.

The majority arose in Syria, Palestine and Egypt, and the greatest morbidity was recorded in December 1942 in Egypt and Eighth Army, where 7·82 per thousand contracted it. For the corresponding period the figures for Palestine and Syria were 4·50 and 2·46 per thousand men respectively. The latter was due to large troop movements and their concentration in chosen sites rather than to any peculiarity on the part of the terrain itself.

Graph I illustrates the epidemiological characteristics of the condition and is constructed from thousands of notifications embracing a large body of newcomers to the Middle East, over a space of three and three-quarter years, scattered throughout a stretch of territory extending from Eritrea to Tripolitania. The curve shows the striking tendency of infective hepatitis to recur annually in the later summer and autumn. Progressive decline in the magnitude of successive annual epidemics was probably attributable to reduction in the scale of military establishments, lesser operational needs, corresponding improvement of sanitary arrangements and healthier living conditions. The gradual development of active immunity through prolonged residence within the endemic area might well have contributed too.

Graph I shows that the Middle East area was a permanent endemic centre of infection and jaundice followed the dysentery season each summer, when the fly menace was at its worst and the maintenance

of effective personal hygiene and sanitation was at its lowest ebb. It is, therefore, not impossible that if sanitary conditions were bad at any place and sufficient susceptibles were present there, the disease could appear at any month of the year.

Immunity of Local Inhabitants.—There is reason to believe that the adult native inhabitants of Palestine, Egypt, Malta and the neighbouring territories are singularly resistant to attack. In Palestine, Cameron (1943) reported that infective hepatitis was an endemic disease of childhood among the local population, whereas British troops who entered the area were soon infected. The same was

GRAPH I.   Incidence of Infective Hepatitis in Middle East Force.

applicable to European Jewish emigrants to Palestine (Btesh, 1944). On the island of Malta, Dixon (1944) found that British troops were twelve times more vulnerable to attack than locally enlisted Maltese. (See also Hartfall, 1944.) In Egypt, during 1941-43, although many thousands of cases occurred among our soldiers, persistent enquiries from local doctors showed that Egyptian civilians were apparently unaffected.

The entry of susceptible newcomers to an endemic area thus reveals the presence of latent infection such as occurred when British troops poured into Egypt during 1941 and 1942. This point was described by Spooner (1943), who referred to the histories of ten field regiments, R.A. in the M.E.F., in the following passage : " Two of these regiments landed in the Middle East in September, or early October, after a jaundice-free voyage. They spent a short time (ten and thirty-seven

days respectively) training and equipping themselves in the Canal and Nile Delta area, and then went into the Alamein line in mid-October for battle, and fought until the end of the first week in November, when after a short rest in the desert, they returned to clean base camps in the Cairo area. Both of these regiments had their main epidemics after returning to the Delta, about a month after battle."

Subclinical Attacks.—Perhaps one of the most significant aspects of the epidemiology of infective hepatitis has been the existence of unrecognised cases in the field. During the North African campaign, Hunt (1944) mentioned that the disease at its onset was one of the important causes of pyrexia of unknown origin, and that many sufferers did not show jaundice. (See also Lisney, 1943 ; Cullinan, 1939 ; Cameron, 1943.) During the siege and aerial bombardment of Malta unique opportunities arose for the study of the malady among the isolated community of British, Indian and Maltese troops, plus their civilian associates. Dixon (1944) emphasised that subclinical attacks were common and, for example, out of six men in a post one might report with jaundice, another with indefinite gastro-enteritis symptoms, and another with diarrhœa. Dixon also went so far as to assert that the prevalent variety of gastro-enteritis, popularly called " Malta tummy," constituted a subclinical variety of the illness. Moreover, during the period of intestinal dysfunction, excessive indulgence in alcohol not infrequently precipitated an attack of jaundice. Hartfall and Damodaran (1944) have amplified the same theory.

Some Inferences.—The circumstances suggest that the virus is ubiquitously distributed throughout the Mediterranean countries ; the local adult population of the latter is immune to attack ; and such resistance is probably acquired during childhood by repeated consumption of food contaminated with virus. Thus we believe that when British troops occupied an infected locality the mechanism of their response to infection resembled that of the local children. Other ranks habitually patronised native cafés and eating-houses and within a short time every man ingested infective material. Some received large doses and developed the typical jaundice, others suffered from pyrexia of unknown origin ; others experienced vague gastro-intestinal symptoms of disease popularly referred to as " Malta " or " Gyppy tummy," without developing jaundice, but in all probability the bulk of the men swallowed subminimal infective doses of virus and so rapidly developed progressive tolerance to successive amounts of live virus.

Susceptibility of Officers.—Spooner (1943) drew attention to the liability of officers to contract jaundice, and he stated that " in certain Eighth Army regiments 8 to 9 per cent. of the total strength of the unit were affected, which often included as much as a third of the officer personnel, who seemed to be 4·7 times as prone to infection as other ranks. The same applied to the Italians. According to some,

alcohol has been blamed, but like Spooner (1943) we are not satisfied it is the whole answer.

Other factors worthy of greater consideration were that although the living conditions of officers in Egypt, during the Middle East campaign, were such as to shield them from mass infection from the external civilian population, their mode of life encouraged its dissemination among the officer class. Officers serving abroad live differently from other ranks. They tend to congregate as isolated communities, patronise the cleanest eating-houses, sleep in the best available quarters, and in general possess the necessary authority to demand the best ablution, sanitary and laundry facilities procurable. On the other hand, because of the isolated and relatively segregated existence which officers pursue abroad, opportunities for the spread of infection from one to another at hotels, social clubs and fresh-water swimming-pools are numerous, not to mention the use of improvised portable bathing facilities designed to conserve water in desert areas.

The cumulative effect of such personal habits is that for a long time after he has entered the country, the officer denies himself the opportunity for intake of subliminal infective doses of virus. The commissioned class so constitute an unprotected herd, and as soon as the first-class case develops in a mess, infection rapidly spreads in the direction of intimate susceptible contacts. Before abandoning this topic the writer feels that in the past, failure to discover the cause of jaundice has attracted too much inquiry to more readily available facts and figures such as, in particular, the susceptibility of officers. We believe that the latter has been accorded exaggerated medical publicity disproportionate to its proper value as useful epidemiological data. The higher incidence among officers was best observed under the particular set of conditions under which they and other ranks lived and fought at the time of the Middle East Campaign. It remains to be seen if the same difference will be repeated elsewhere.

Mixed Units, Air Crews, and Civilians in Britain.—If the above explanation were right, in circumstances where officers and men serve together one would expect the incidence of the disease to be similar. This may be so with air crews (see Havens, 1944). Since infective hepatitis virus has been demonstrated in stools, it is obvious how men could become infected in flight, where ablution facilities are limited and water rationed, particularly in view of the recent claim by Findlay and Willcox (1945) to have demonstrated the virus in urine.

Again, if our line of reasoning were correct, in Great Britain where the standards of living and sanitary arrangements were of a relatively uniform type, class selection should be absent. Epidemics are commonest among school children and hospitals, but in general class distinction is lacking, the disease spreads by personal contact indiscriminately of age, sex or what section of the community the individual may belong to, civilian or military (see Ford, 1937; Cullinan, 1939; Newman, 1939; Lisney, 1943; Evans, 1942; Cookson, 1944).

For practical purposes the population in Britain can be regarded as susceptible less a few adults who have derived immunity during childhood. Table I clearly demonstrates that troops from the British Isles are more receptive to jaundice than men from other parts of the Empire. The situation can be contrasted with the cosmopolitan Middle East, where the virus is ubiquitously distributed so that instances of case to case contact infection are difficult to trace, because the level of adult mass immunity is high.

Blood transfusion work during the war has illustrated how easily blood and plasma derived from apparently healthy men may become icterogenic, from contamination with either serum jaundice or infective hepatitis virus. If further research should prove these two agents to be identical, the finding of infective hepatitis virus in fæces reveals the limitless possibilities for spread of infection in warm climates.

Prevention of Epidemic Infective Hepatitis.—In theory, attention should be paid to every obvious source of potential infection, but in practice this is impossible to achieve. Prompt recognition and segregation of early cases masquerading as mild pyrexia of unknown origin, or gastro-intestinal disturbances of indefinite type, routine biochemical examination of blood, urine, and the employment of skin tests for detection of latent jaundice may assist (Cullinan, 1939, and Havens, 1944). The resistance of the virus of infective jaundice (presumably identical) to physical and chemical agents coupled with its high degree of infectivity introduces a fresh crop of difficulties.

The virus of serum jaundice traverses bacteriological filters of the Seitz and Berkefeld types, it withstands equal volumes of phenol and ether of 0·5 per cent. concentration for many months ; resists heating at 56° C. for one hour or drying and freezing for several weeks (Memorandum, 1943).

The severity of the resulting disease was not related to the dosage of inoculum administered, and as little as 0·1 c.c. of serum or the prick of an infected needle has been known to convey infection (Bradley, Loutit and Maunsell, 1944 ; and Salaman, King, Williams and Nicol, 1944).

Recent work indicates that infective hepatitis virus has similar biological properties (Havens, 1945), and its existence in stools (and possibly also in urine) introduces some herculean difficulties of field sanitation.

The hygiene of most units of the M.E.F. was excellent, judged according to the dysentery rate, but far more was demanded to deal with infective hepatitis. In the desert campaigns, the Army Hygiene Services accomplished a magnificent task under trying conditions, and the reader should not omit to read the classic description of the situation given by Richmond and Gear (1945). It was impossible to control the spread of infective hepatitis under such conditions. Perhaps, in future, something can be accomplished by unit propaganda and an appeal to all ranks to improve their personal hygiene such as by the washing of hands after defæcation, urination, and prior to taking

TABLE I

Incidence of Infective Hepatitis among different Troops throughout Egypt, Cyrenaica, Tripolitanea, Palestine, Syria, Cyprus, Sudan, Eritrea, Malta and Aden expressed as Total Admissions to Hospital and as Ratios per 1000 Strength for the Year 1943

	United Kingdom.		New Zealand.		Union Defence Force.		Indian.		British African.		Other British.		Others.		Total Cases.	
January	2098	5·62	105	3·37	42	1·36	79	0·99	58	1·36	...		449	4·26	2831	4·27
February	664	1·87	35	1·12	21	0·71	50	0·69	18	0·44	...		46	0·66	834	1·39
March	369	0·85	18	0·59	9	0·39	37	0·41	7	0·15	...		39	0·49	479	0·70
April	245	0·59	16	0·51	12	0·52	30	0·41	6	0·10	20	0·40	18	0·49	347	0·51
May	195	0·41	8	0·24	5	0·11	23	0·25	8	0·14	14	0·37	22	0·37	275	0·35
June	195	0·42	16	0·59	28	0·60	17	0·17	8	0·10	21	0·50	32	0·51	317	0·39
July	305	0·77	24	0·90	11	0·24	28	0·30	11	0·20	16	0·38	29	0·43	424	0·58
August	321	0·87	27	0·85	12	0·27	38	0·38	20	0·35	23	0·55	43	0·67	484	0·68
September	451	1·34	36	1·09	32	0·61	34	0·37	12	0·20	37	0·91	41	0·46	643	0·91
October	889	3·17	16	0·98	32	0·58	37	0·49	16	0·29	35	0·87	257	2·40	1282	2·03
November	567	2·34	12	1·00	19	0·37	46	0·48	22	0·39	40	0·92	397	4·46	1103	1·87
December	515	2·05	9	0·92	22	0·40	58	0·82	27	0·49	32	0·72	375	3·59	1038	1·76

Figures compiled by O.C. Medical Statistics G.H.Q., M.E.F., and reproduced by permission of D of P War Office.

food. Notwithstanding such counsel many major vehicles of potential infection will continue to pass unchecked, namely, bedding, linen, clothes, towels and unprotected food and water. Under war conditions appropriate remedial measures are hard to effect. The highest incidence of hepatitis in the Eighth Army in the desert was approximately 8 per 1000, and to combat this single item the requisite labour to disinfect the garments of so many men would have been disproportionate to the reward in prospect.

Infective Hepatitis and Poliomyelitis

Accounts of recent work on poliomyelitis in the Mediterranean Zone and India shed light on the pathogenesis of infective hepatitis, and the two appear to share something in common. In Egypt, Paul, Havens and van Rooyen (1944) isolated poliomyelitis virus from the fæces of no less than nine out of ten fatal cases in British and American troops. Cases occurred among local children, but fulminating infections resembling that observed in newly arrived European soldiers could not be traced in the adult Egyptians, civilians or soldiers. In a critical report on poliomyelitis in India Command (McAlpine, 1945) has pointed out other epidemiological features equally applicable to infective hepatitis.

McAlpine (1945) states that " Acute poliomyelitis among British troops in India is mainly a disease of hot-weather months, thus coinciding with the season of flies and dysentery ; this fact suggests that there may exist one or more factors common to the epidemiology of these two conditions. The explanation of the striking fact that the disease is five times more common in British officers than in other ranks in India should provide the key to the problem of transmission in that country."

On the Gozo island of Malta, during November 1942 and February 1943, the incidence of fatal poliomyelitis was 19 per cent. in service cases as against 3·5 per cent. in civilians. McAlpine (1945) also emphasised that the disease was four times as frequent in the R.A.F. as it was in the Army. Seddons et al. (1945) have expressed the opinion that the Malta outbreak was not imported by service personnel. The authors would point out that before the epidemic started in November 1942 in Malta, 106 cases (33 fatal) including Army, Navy and Air Force personnel, British and Dominion,. had been reported from Egypt, Palestine and Syria during 1941 and 1942. In May 1942 van Rooyen and Morgan (1943) isolated a highly virulent strain of poliomyelitis virus from a fatal case occurring in Egypt, and forwarded it for examination to Schlesinger, Morgan and Olitsky (1943) at the Rockefeller Institute, New York, where the virus was found to resemble the Lansing strain by its pathogenicity to the American cotton-tail rat. Fear of its importation from Egypt to the besieged fortress of Malta by air was clearly anticipated in the following statement by van Rooyen and Morgan (1943): " There is always the chance that,

although the disease may not attain epidemic proportions under one set of living conditions, if it did reach a closed community such as an isolated island, all factors favourable for an epidemic may arise." Bernard (1945) of Malta also expressed the conviction that poliomyelitis was introduced by airmen to the island at the time of its heroic struggle.

Seddons *et al.* (1943) have concluded that infection was spread in Malta by naso-pharyngeal droplet contact, assisted by over-crowding. Our experiences in Egypt have resembled those of older epidemiologists, namely, that in a susceptible population housed over a large enough area, cases can arise spontaneously at isolated points many miles apart. Modern work indicates that poliomyelitis virus is more easily recovered from stools than from naso-pharyngeal secretion. (See Trask *et al.*, 1938, 1940, 1943 ; Kramer *et al.*, 1939 ; Sabin and Ward, 1941 ; and Paul, Havens and van Rooyen, 1944.)

In the Orient, opportunities for the dispersal of fæcal infection, be it infective hepatitis or polyiomyelitis virus, are unrestricted, and infection is likely to be massive when it does occur. The consumption of uncooked food and vegetables, however well they may be washed in the average public or private kitchen sink, is an ever-present danger to consumers and others whose utensils may become contaminated through their presence. Human night soil (dried fæces) has been used from time immemorial as a cheap fertilizer by native cultivators throughout a great part of the tropical and sub-tropical world. One of us has repeatedly watched lettuce, celery, tomatoes, onions, water mellons and cucumber fruit gathered by peasants at a smallholding, " washed " in the stagnant unpurified communal sewage effluent of the local village and subsequently served up as " delicious " salad on the menus at fashionable hotels and officers' messes in the nearest towns.

Before it is possible to appreciate the underlying nature of these two virus diseases one should abandon older ideas which persistently endeavour to explain their epidemiology by case to case contact oblivious of the existence of powerful immunity effects. Both infective hepatitis and poliomyelitis are primarily intestinal maladies. The carrier as well as the immunity rates at the time of an epidemic have never been accurately surveyed for lack of convenient methods ; but enquiry may well reveal them to be higher than generally supposed in certain localities. Susceptible individuals who ingest infective hepatitis virus develop the secondary complication of jaundice more frequently than do these who develop secondary paralytic phenomena after ingestion of poliomyelitis virus.

DISCUSSION

The relationship of infective hepatitis to serum jaundice, post-arsenical and post yellow-fever vaccine jaundice remains a mystery. No laboratory animal has been found susceptible to infection with any of these varieties of jaundice. A continuous supply of human

volunteers is unobtainable and, even if available, experiments on man are irksome because the incubation period is lengthy, it is hard to control tests so as to eliminate the chances of accidental infection, subicteric attacks may evade recognition, and there is no method of detecting immune persons.

Bigger (1943) has demonstrated that jaundice following anti-syphilitic treatment was due to faulty sterilisation of syringes and needles contaminated with homologous serum jaundice virus. Sheehan (1944) and Salaman et al. (1944) and others have provided confirmation.

Dible and McMichael (1943) studied the histopathology of liver biopsy tissue from cases of arseno-therapy jaundice, and concluded that the appearances of the organ were more compatible with damage by an agent similar to that causing serum jaundice or epidemic hepatitis.

Histological methods of examination thus fail to differentiate between post-arsenical jaundice and infective hepatitis. The incidence of post-arsenical jaundice in the Mediterranean theatres of war has been singularly high. The discovery of infective hepatitis virus in stools points to the alimentary tract as the initial site of infection, and raises the obvious question as to how widespread infection has been, and to what extent arsenic has aggravated undetected liver damage caused by inapparent infective hepatitis.

Histological study of gut tissue from early cases of infective hepatitis in the febrile and pre-icteric phases of the illness might reveal specific changes, but death does not occur prior to onset of jaundice, and the information solicited may not be obtainable.

Hepatitis following injection of mumps convalescent plasma has been extensively studied by Beeson et al. (1944) and Hawley et al. (1944), and a wide range of human blood products and derivatives employed for transfusion or immunisation have been shown to contain jaundice virus (Morgan and Williamson, 1943). Likewise, post yellow-fever jaundice seems to be due to contamination of tissue cultures with human serum containing serum jaundice virus (see Badger, 1943). Oliphant, Gilliam and Larsen (1943) demonstrated that the icterogenic agent in yellow fever vaccine was filterable, survived drying in vacuum, storage for long periods at 4° C., resisted heating at 56° C. for thirty minutes in the dry state and could be inactivated by exposure to ultra-violet irradiation. Infective hepatitis virus displays similar physical properties according to Havens (1945) and Paul et al. (1945).

The relationship of serum jaundice to infective hepatitis presents a conundrum, for if it were eventually proved that the two were identical then the existence of subclinical silent blood-borne infective hepatitis would claim fresh significance.

Some believe that they are ætiologically different because infective hepatitis is spread by contact and has an incubation period of twenty-eight to thirty days, whereas clinical serum jaundice is normally caused by parental administration of icterogenic serum, has an incubation

period of eighty to a hundred days according to Paul *et al.* (1945), Steiner (1944) and Beattie and Marshall (1944). The latter also discovered that it was possible to reduce the incubation period of serum jaundice to thirty days by feeding infective serum. Evidence in favour of their identity has been provided by Sheehan (1944), who noticed that infective hepatitis virus may be conveyed from one man to another by unsterile needles and syringes used for aspirating blood, and that the ensuing malady assumed the character of typical serum jaundice after an incubation period of three months. Efforts to isolate virus from the fæces of serum jaundice cases by MacCallum (1945) and Neefe, Stokes and Gellis (1945) have been unsuccessful, and it therefore seems that the intestinal tract contents are not infective in serum jaundice. Oliphant (1944) pursued a different angle of approach and from a small series of cross immunity neutralisation tests on human subjects inferred that one attack of serum jaundice protected *against* a second, from *in vivo* and *in vitro* tests. Also an attack of serum jaundice conferred immunity against infective hepatitis.

Conclusions of the opposite kind have been reported by Paul *et al.* (1945), who found that three patients who had recovered from serum jaundice six months earlier, later proved susceptible to experimentally induced infective hepatitis. The latter have epitomised the present position by stating that the outstanding difference between serum jaundice and infective hepatitis rested in the length of the incubation period. Neefe, Stokes and Gellis (1945) likewise showed that individuals who had recovered from serum jaundice were resistant to parenteral inoculation with the same agent, but were susceptible to oral administration (but not parenteral injection) with infective hepatitis serum or filtered fæces. Neefe, Stokes and Gellis (1945) have commented that " Normal persons are much more likely to develop the disease when the agent is administered orally than when it is injected parenterally," a fact which we regard as one of fundamental importance in the establishment of infective hepatitis as a primary pathological affection of the gut.

The two diseases may be closely related in that serum jaundice represents the artificial production of infective hepatitis in a proportion of instances : it cannot yet be said that all serum jaundice belongs to this category. The question of the ætiology of post-arsenical serum jaundice and infective hepatitis bristles with unsolved academic problems and practical obstacles to progress, but the subject is of as much interest in peace as in war and justifies intensive research into the pathogenesis of these icterogenic virus agents.

SUMMARY AND CONCLUSIONS

The epidemiological behaviour of infective hepatitis has been interpreted in the light of the recent discovery of the causal virus in human stools. Special reference has been made to the spread of infection under conditions which British troops served in the Middle East Force.

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SOME ASPECTS OF A PLASTIC SURGERY UNIT *

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THE development of the faculty to "diagnose" is the first essential to the plastic surgeon. Tissues can be displaced, tissues can be destroyed, or there can be a combination of both states. Loss or distortion of the soft tissues can be estimated only when the state of the underlying bony structure is known. On an accurate diagnosis rests the foundation of proper structural repair. The majority of the failures in plastic surgery are due to inadequate preliminary examination.

Many factors may influence the plan to be adopted, *e.g.* age, sex, physical and mental health, importance to war effort, etc. ; the time elapsed since the injury may affect the method of reconstruction.

The principles and illustrations of the more common plastic procedures which could be adopted are outlined.

Assuming the knowledge of the various types of free skin grafts and flaps with the technique employed, the first question to be answered is, when should a graft be applied ?

When Should a Graft be Applied ?

Immediate . .	(a) Traumatic amputation of the finger.
	(b) In skin loss.
	(c) In flap wounds.
	(d) In compound fractures.
	(e) With exposed tendons.
	(f) In certain burns (i) Localised deep burns.
	(ii) Electric and Chemical burns.
At the first opportunity.	(a) In burns : (i) Open Methods
	(ii) Closed Methods { Coagulants. Pressure with Immobilisation.
	(b) Contaminated or granulating wounds.
	(c) Lupus.
To relieve deformities.	(a) Congenital anomalies.
	(b) From (traumatic) skin loss.
	(c) From chronic inflammations.
	(d) Contracted eye sockets.

I. IMMEDIATE, OR ACUTE EMERGENCY GRAFTING

E.g. in casualty and routine surgical work. If a primary closure in a wound with loss of skin is desired, skin grafting is indicated.

. (a) *Traumatic Amputation of Finger.*—A common type of industrial injury is traumatic amputation through the terminal or

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* A Honyman Gillespie Lecture, given in the Royal Infirmary, Edinburgh, 5th October 1944.
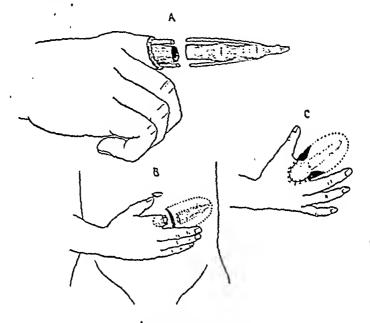
other phalanges. It is a serious type of injury, since it leads to loss of man hours in skilled workers. In many instances the wound is left to granulate ; the exposed bone becomes infected, sequestrates, and eventually a thinly covered painful scarred finger-tip is left.

The treatment suggested is immediate covering by (i) a local flap with a thick razor graft to secondary defect ; (ii) a thick razor graft ; or (iii) a flap from the palm or from opposite forearm or abdomen.

Traumatic amputation through the proximal phalanx leads to a further possibility, that of autografting.

The severed finger is cleansed, and the skin, subcutaneous tissue and nail dissected free and discarded. The denuded finger is then

AUTOGRAFT OF FINGER.
FIG. 1.
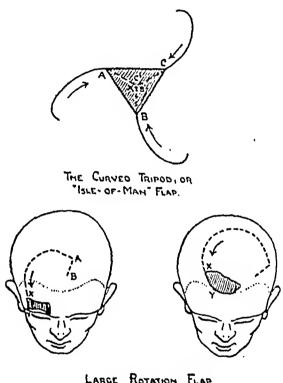
embedded just below the skin at a suitable site of the abdomen or thigh. The wounds of the finger and abdomen are closed. Later the continuity of the finger is re-established by reconstituting the skin of the stump and the tendons to the embedded digit. Three weeks later sufficient skin to cover the finger is raised and the repair completed.

Patient I. L., aged 4, dropped a heavy grating on the fingers of his right hand. His right index finger was almost completely severed at the base of the proximal phalanx. Following admission the finger was amputated and the stump covered with local flaps. The skin and nail of the amputated digit were removed and the finger then embedded immediately under the skin of the abdomen. Some weeks later the stump was re-attached to the embedded digit, bone to bone and tendons to tendons. In three weeks' time sufficient skin was raised around the index and the finger re-established (Fig. 1).

(*b*) *Where there has been Skin Loss.*—The surgeon must appreciate the delay in healing and the deformities that may arise if skin is not applied immediately to a raw area following skin loss, and the danger of yielding to the temptation to close under tension rather than to apply an emergency dressing of skin.

A comparatively common accident is the slicing injury with loss of skin, *e.g.* from the thenar eminence. If the original tissue can be obtained this may be applied in the form of a whole thickness graft, if not, a thick razor graft is used to cover the defect.

In scalping accidents, the defects are closed by local flaps or thick razor grafts ; in this injury the original tissue will not survive if it is replaced.

THE CURVED TRIPOD, OR
"ISLE-OF-MAN" FLAP.

LARGE ROTATION FLAP
FIG. 2.

Small defects are closed by the curved tripod or Isle-of-Man flap, larger defects by the sliding rotation flap or by a free graft.

In the curved tripod all three sides of the triangle form the swinging side of a rotation flap.

The larger defects can frequently be considered as triangular, and the plastic rotation swings across the shorter side XY (Fig. 2). The flap incision sweeps from X to a point A ; this permits of swinging : to allow rotation, the incision turns sharply from point A towards the defect as far as is necessary to eliminate tension along the suture line.

D. B., aged 36. Patient received a gun-shot wound in the right frontal region on 20.7.43 in Sicily. Some fragments of frontal bone were driven

into the frontal lobe. Debridement of the brain track was carried out and penicillin applied. A razor graft was applied directly to the dura. The problem was to cover the soft defect with a flap and later the bony defect with a bone graft. A large rotation flap which advanced the frontal hair line was employed. A free graft closed the secondary defect. At a later date a bone graft was inserted.

Thick razor grafts should be applied to any areas of considerable skin loss in the face. At a future date a plastic surgeon can be consulted to carry out a secondary repair if thought advisable.
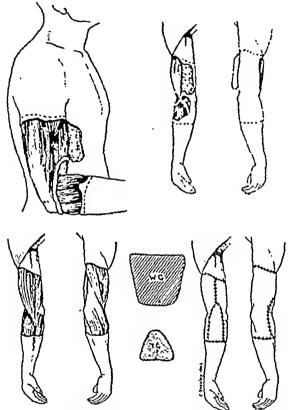
FIG. 3.—Steps in procedure in flap wound.

Following excision of the breast, the raw bed can be covered, without tension, by means of a razor graft.

(c) *Procedure to be adopted in Flap Wounds.*—From time to time the flap type of wound is seen in casualty work. The flap may consist of skin or skin and subcutaneous fat. If of skin only, then the flap, after thorough cleansing, should be stitched back in position and a pressure dressing applied. The flap, which consists of skin and fat, is a different problem. The first point to decide is the viability and vitality of the flap. The local circulation may be gauged by the simple method of digital pressure. A good venous return is as important as a good arterial supply. A " blue " flap is a more serious danger sign

than a " pale " flap. Where the vitality of the flap—no matter the area involved—is questioned, the flap should be detached completely and removed ·to a side table. ' There the fat is cut off and the flap converted to a whole thickness free skin graft; the skin is then replaced and stitched into position and a pressure wool dressing applied.

I. McI., aged 4. On 12.2.42 patient was run over and received extensive soft tissue injuries to the right upper arm. The skin from the insertion of the deltoid to the mid forearm was in part hanging as a flap and the remainder tunnelled from the deep fascia. The flap and the tunnelled portion of skin was

AREA FOR GRAFTING
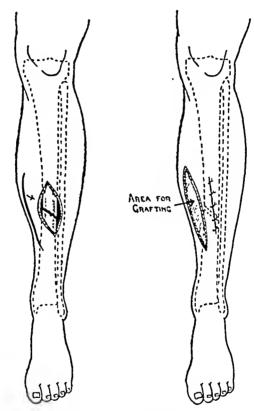
FIG. 4.—Swinging flap.

excised in one piece and at a side table was converted into a full thickness graft by removing the fat. The skin was stitched back as a freegraft. The result was satisfactory from the point of view of take and ultimate function (Fig. 3).

If this procedure is not adopted, death of the flap in whole or in part is liable to occur. Several patients have been admitted with large necrotic flap wounds, especially of the extremities. Hospitalisation in such patients is prolonged ; yet, as can be seen, this is avoidable, in most instances, with adequate early surgery.

(d) *Compound Fractures*.—With American orthopædic units there is an associate plastic surgeon. Experience has indicated that in compound fractures, where there has been skin loss, a thick razor graft is best applied immediately following reduction ; then the limb is encased in plaster. Where the tibia has been involved a swinging flap

is advanced to cover the superficial antero-medial aspect of the shaft and the defect posteriorly is covered with a thick razor graft (Fig. 4).

(e) *Exposed Tendons.*—One of three procedures can be adopted.

> (i) An immediate skin graft.
> (ii) An immediate skin flap.
> (iii) Allow the wound to granulate then apply a skin graft.

Where the tendons are obviously dead, their excision must be carried out before grafting. Where the vitality of the tendons is questioned, the employment of a skin flap, with its established blood
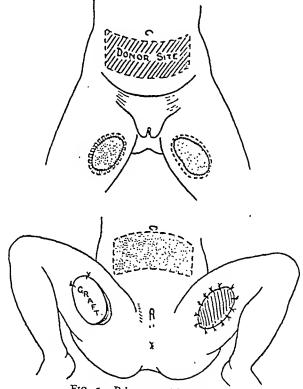
FIG. 5.—Primary excision of burn.

supply, will give a greater chance of their recovery. Where the tendons are uninjured, the application of a thick razor graft or dermatome graft is indicated. If the surface contour is very uneven, a tulle gras dressing is applied followed by plaster of paris. In ten days the plaster is removed. Granulations will have formed a flat surface, and a thick razor graft can be applied.

(f) *Burns, in Selected Cases.*—(i) Localised deep burns.
Excision of the burn with immediate grafting is the procedure to be followed.

A baby, I. T., aged 9 weeks, was admitted with a deep circular burn 2½ in. in diameter on the medial aspect of the upper third of both thighs

resulting from the prolonged application of a cinder. To prevent frequent painful dressings excision and grafting were carried out.

Following excision of skin and fat, a dermatome graft was cut from the lower abdomen and the raw areas on the thighs covered with skin. Pressure dressings of wool were applied and the lower limbs fixed in plaster in the "frog-position" to prevent soiling of the grafted areas. The take was very satisfactory and the patient was in hospital for four weeks only (Fig. 5).

(ii) Certain electric and chemical burns.

Where possible excision of all the affected tissue is carried out and followed by immediate grafting.

II. At the First Opportunity

(*a*) In burns treated by : (i) *Open Methods.*—Tulle gras and saline form a satisfactory dressing for deep burns of the face, since sepsis can be controlled and the separation of sloughs observed and aided. Thin razor grafts are applied at the earliest moment, especially to the eyelids to prevent ectropion. The importance of the early application of grafts to the face and hands in burns must be more widely recognised. Severe degrees of contractures are prevented and the final repair facilitated.

A. McM., an engineer, aged 21, one month before admission fell face downwards into the fire and received severe extensive deep burns. He was treated with sulphanilamide ointment. One week later the raw areas were covered with dermatome grafts ; three weeks later the eyelids were grafted and sewn together.

(ii) *Closed Methods.* (*a*) Coagulation. When a tan remains adherent three to four weeks, the area covered must be considered one of loss of the whole depth of skin. Before sepsis gains entrance at the line of demarcation between the living and dead tissue, the coagulum should be excised and a thick razor or dermatome graft applied.

Patient G. M., a member of R.N., aged 21, was burnt on 30.4.42, affecting mainly his left thigh. The burn was coagulated. On admission on 7.6.42 the tan on the thigh was still adherent ; it was excised and grafted ; the take was 100 per cent. ; at least four to six weeks' hospitalisation was prevented.

(*b*) Pressure and Immobilisation. For over eighteen months early burns of the forearm and hands have been treated by light, carefully controlled pressure dressings—the pressure is in the region of 10-15 mm. Hg.—elevation and absolute immobilisation in plaster of paris. The plasters are removed in ten to twelve days ; if the slough on deep burns has separated, the plasters are not re-applied and the wound is conditioned prior to grafting. The aim is to have all deep burns grafted in from three to four weeks from the time of the accident. The skin of the palm has a specialised type of epithelium that produces a thin keratin layer for protection and has a thin derma ; it heals poorly following burns which even where rather superficial may produce contracture deformity.

There is one important point in the care of burns of the hands, that is appreciated in part, but is seldom actively controlled, namely, the correct positioning of the thumb. The thumb is abducted from the palm and lies opposite the index finger *facing* the other four fingers. I know of no method, apart from pressure dressings and plaster immobilisation, which will maintain this position. The importance of this fact arises in the control of deep burns. So often burnt hands are left to lie on a pillow; gravity and the upward counter-thrust of the pillow push the thumb in line—not opposite—with the index finger, and the thumb looks across the palm. The bad positioning of the thumb leads to very difficult and not uncommon problems to the plastic surgeon.

(c) Contaminated or granulating wounds with or without exposed tendons. A course of preliminary cleansing is instituted. When tendons are exposed the formation of granulations is encouraged by leaving the part under plaster of paris for ten days. A thick razor graft is applied when the surface is considered to be receptive.

Granulating surfaces must be carefully examined and intelligently treated. If granulations are unhealthy, they are tender; there is no epithelial response at the perimeter and the edges are covered with the crusting of former local applications, or discharge; the surface is usually irregular, exuberant, pinkish-yellow in colour, with small local collections of exuded pus. The infecting organism may be the staphylococcus aureus, or albus, the streptococcus pyogenes, the bacterium coli, the ps. pyocyaneus, or the bacillus proteus. Most of the infection is in the surface layer, but does extend throughout most of the granulation tissue.

Healthy granulations, on the other hand, are not tender; the edge demonstrates the healing response; the surface level is flush with the skin and regular, and the colour is pinkish-red or red.

Many methods can be adopted to prepare an infected granulating surface; a few will be described.

After cleansing the adjoining skin with soap and water or " Cetavlon " (CTAB/1·5 per cent.) and removing all crusts from the edges, the raw area is covered with tulle gras and swabs wrung out of normal or hypertonic 3·5 per cent. saline. The swabs are changed every two to four hours, the tulle gras once daily. If the swabs tend to dry they should be covered with jaconette or oiled silk. Sir Almroth Wright advised the use of a 5 per cent. solution of common salt mixed with ½ per cent. of sodium citrate. This is a lymphagogic solution and renders the lymph incoagulable. All dressings are kept in place with a firm crêpe bandage to maintain pressure. If necessary a sponge rubber can be interpolated between the turns. Where the discharge is copious the saline dressing is alternated with half strength eusol. During the sleeping hours the dressings are kept moist with saline or eusol poured from an undine.

Rest, elevation and pressure are the fundamentals in the preparation

of the recipient area. Moist dressings with pressure are adequate counters for exuberant granulations; caustic applications are never necessary.

Where the infection is proved to be streptococci, sulphanilamide or sulphathiazole powder applied prior to tulle gras is useful. In staphylococcal and sulphonamide resistant streptococcic infections, propamidine, a buffered-proflavine in sulphathiazole (1 in 99) powder, and local penicillin (1000 units per gram) are of great benefit. The powders are applied by means of insufflators and covered with tulle gras and gauze wrung out in normal saline. The powder is reapplied once or twice daily. At every dressing when the tulle gras is removed, the surface is gently cleansed with a moist wool pledget and then a culture swab is taken. To remove gram-positive organisms by local applications, penicillin is undoubtedly the most potent weapon available.

If sloughs are present a thrice-daily dressing of half or whole strength eusol is efficient.

In areas infected by gram-negative organisms, a thrice-daily application of 1 : 1000 solution of buffered proflavine-sulphate under jaconette may prove beneficial, or the proflavine in sulphathiazole powder. Other applications suggested are 1 : 1000 alcoholic merthiolate solution and 1-5 per cent. acetic acid. Zinc peroxide has been found a useful local application especially in micro-ærophilic streptococcal infections. Unfortunately it is difficult to obtain; it is prepared by Dupont and distributed in the United States by Mercke & Mallinkrod. The powder must be activated by dry heat before use.

The criterion for a receptive granulating surface is not necessarily a negative bacteriological culture but a healthy surface from the clinical point of view.

(d) Lupus. Free grafts have an apparent immunity to lupus. In selected cases the disease can be eradicated and its stigmata avoided by excision and grafting. Sir Henry Gauvain at Lord Mayor Treloar Hospital has a plastic surgeon on his staff who treats lupus successfully.

J. B., aged 28, a service patient with extensive lupus. Affected areas on face and forearm excised and covered with thick razor grafts.

III. To Relieve Deformities, *i.e.* Late Grafting

(a) From congenital anomalies, *e.g.* syndactyly. In congenital syndactyly there is sufficient skin locally to form the base of the web only. The raw areas on the sides of the fingers are covered with free grafts (Fig. 6).

(b) From skin loss, *e.g.* war wounds and burns. The deformities are, of course, many; in addition, the covering scar epithelium has no pad of dermis to attach it to the subcutaneous tissue and is not serviceable as a bearing surface. It is thin, devoid of papillæ, hair follicles and glands, and may form an excessive layer of keratin. Since this epithelium never becomes firmly attached to the underlying fibrous

FIG. 7a.—Before treatment.

FIG. 7b.—After treatment.

FIG. 8a.—Before treatment.

FIG. 8b.—After treatment.

FIG. 9a.

FIG. 9c.

FIG. 9b.
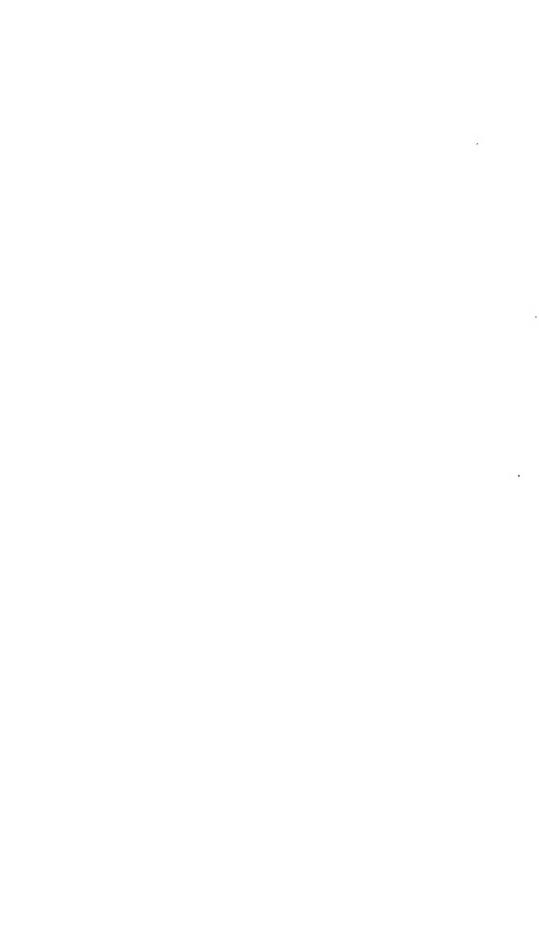
FIG. 9a.—Before operation.
FIG. 9b.—Cross-leg flap attached.
FIG. 9c.—After operation.
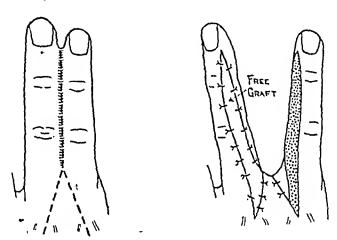
tissue, large areas can be detached and lost by trivial injuries or infections.

The principle in treatment is the recreation of the original defect by excision of the scar tissue and the replacement, into correct position, of what is normal. To cover the resultant defect, first a local flap is considered ; if this is not practicable, a flap from a distance is employed. The secondary defect is covered with a thick razor graft.

The following cases typify the methods of plastic repair in the many forms of war casualty.

Sgt. R. W., a regular soldier, in the retreat to Dunkirk was shot through the upper jaws and cheeks. The defects were repaired by various local flaps, plus a buccal inlay to bring forward the upper lip (Figs. 7a and 7b).

REPAIR OF SYNDACTYLY

FIG. 6.

D. McE., aged 33. Patient was wounded on 10.9.43. He received wounds of both buttocks penetrating through to the perineum. These healed with the formation of a fibrous perineal web, which prevented the patient sitting down, and limited abduction. The scar was excised and the posterior half of the scrotum used as a local flap to close the defect.

D. D., aged 21, a member of the R.A.F. Ten months before admission patient received severe burns of both hands, face, neck and upper chest. The most marked deformity was the webbing of the neck and ectropion of the lower lip. This was treated with dermatome grafts (Figs. 8a and 8b).

J. M., aged 20, a munition worker who was severely burned following an explosion. She was admitted nine months later with severe deformities of face and hands requiring grafting. All operations consisted on free grafts, dermatome and dissected.

I should like to mention at this point the help given by Mrs Dove, of Elizabeth Arden, Jenners Ltd., who attends every week to help us

to mask minor degrees of disfigurement and to add colour to pale grafts and tone down the ones more stained. The results are excellent.

A. H., aged 24, a service patient who had a troublesome old burn scar of the dorsum of the right foot. This was treated with a cross-leg flap (Figs 9a, 9b and 9c).

(c) From inflammations, e.g. lupus and syphilis. Both are characteristically destructive diseases as seen by the plastic surgeon, and frequently involve the nose. Lupus, in time, causes through and through destruction, and a rhinoplastic repair is necessary. In the syphilitic nose there is destruction of the nasal mucous lining, and an intra-nasal skin graft is required to relieve the deformity.

S. K., aged 37. Partial destruction of nose and upper lip. Treated by forehead flap and buccal inlay.

(d) To reline eye sockets. An eye socket lined with conjunctiva may cause considerable inconvenience with profuse discharge and gradual decrease of size of the cavity. This can be eliminated by excising the conjunctiva and lining the socket with a razor graft from the inner side of the upper arm.

OBSERVATIONS ON TREATMENT OF FRACTURES OF THE FEMUR *

By E. A. JACK, *O.B.E.*, F.R.C.S.Ed.

OVER two thousand years ago Hippocrates wrote with reference to fractures of the femoral shaft that two strong men should suffice to make extension and counter-extension whilst a bandage was applied. The principle of preliminary reduction followed by fixation is probably as old as these fractures themselves. There is little record of any notable departure from that method until 1875. In that year, Hugh Owen Thomas applied the use of his bed knee splint to the treatment of this fracture, and evolved the principle of a sustained longitudinal force to stretch the muscles through the medium of extension plasters applied to the skin. By frequent and regular tightening of the tapes, the shortening could be overcome and the limb restored to its proper length.

At the beginning of the present century, the introduction of skeletal fixation by the Kirschner wire, the Steinman pin and the Pearson ice-tong caliper started the trend of continuous weight and pulley traction which was developed so widely during the 1914-1918 war. The weight was in continuous action and did away with the necessity for frequent and regular tightening of extension tapes, and considerable weight could be applied to tire out the strong thigh muscles, pull the fracture into line and hold it there. The principle of initial reduction tended to fall into abeyance with these methods of traction. Many modifications were elaborated mainly involving the suspension of the limb. The Pearson knee flexion piece was added to the original Thomas splint ; Hodgen's splint, the simple sling of Hamilton Russell, Braun's frame, the hanging cast described by Farquharson—all provided support for the limb while the weight did its work.

A perusal of the text-books on surgery in general and fractures in particular shows that in the period between the wars the use of continuous weight and pulley traction was taught in the majority of schools and adopted in most hospitals as the method of choice. An occasional voice was heard from the disciples of H. O. Thomas faithfully preaching the principles of fixed skin traction which he had taught. But it was rather a voice in the wilderness. The continuous application of a heavy weight seemed much more attractive and efficient. Possibly Watson Jones may have evoked some surprise when he was found to state that most fractures of the shaft can be treated satisfactorily in a Thomas knee splint with skin traction.

He does, however, recommend one departure from the original method of Thomas : he stresses the importance of adequate reduction under anæsthesia before the limb is put up in the apparatus.

The present observations are based on the experience of a large number of these fractures during the recent war, mainly in an Orthopædic. Centre in the Middle East between 1941 and 1943. It was with a background of orthodox teaching that they were approached, and at first they were all treated by continuous weight and pulley traction. But as the battles waxed and the number of casualties increased, it became a common state of affairs to have twenty-five such cases in one ward, and the difficulties and shortcomings of the method soon made themselves only too apparent. Due to the influence of the late Brigadier Eastwood who was consultant orthopædic surgeon at that time, the principles of fixed traction in a straight Thomas splint were adopted as an alternative and certain modifications to the standard method were introduced. The difference was very striking both in the ease of management and in the ultimate results, and it gave much food for thought. Some of the views expressed here have already been published in a paper by Charnley (1944) who was associated in the treatment of some 130 of the cases, but they seem of sufficient importance to warrant reiteration.

The complications of fractures of the femur fall into three groups :—

(1) *Deformity*.—This includes shortening, lateral angulation, posterior angulation, or internal rotation of the knee and foot. These are the result of muscular action. Almost all .the long muscles that pass from the pelvis to an attachment below the fracture lie obliquely to the femoral shaft on the medial side. In particular, the medial hamstrings and adductor magnus tilt the lower fragment medially. Gravity and the gastrocnemius draw it backwards. The upper fragment is influenced mainly by the glutei and psoas which tilt it laterally and forwards and may produce external rotation. The muscles are at first inhibited from voluntary motion and soon waste, so that in a week or ten days the bulk of the thigh is very much reduced and the power of the muscle pull correspondingly diminished. At first the hæmatoma does not give any support to the bone ends, but after two or three weeks early callus begins to fuse the fracture and movement of the fragments in a longitudinal direction is prevented. The callus is still plastic, however, and leverage easily produces angulation. At five to six weeks union is often firm enough to permit the leg to be raised from the splint, but repeated leverage will still slowly bend the bone. At this stage there is no pain and voluntary muscular activity has returned. Unless the bone is still protected, the preponderance of muscles on the medial side is very apt to produce a late angulation. There is no excuse for deformity. It is preventable by good treatment.

(2) *Interference with Union*.—In the straightforward case the femoral shaft has a natural aptitude for union which is often embarrassing to the surgeon. It may catch him unawares before he has achieved

his object in restoring length and line. Delayed union in the absence of infection is occasionally due to interposition of soft tissue, but much more often it is the result of distraction of the fragments or lack of immobilisation. Non-union is extremely rare. These complications are almost always the direct result of bad treatment.

(3) *Restricted Function.*—This is usually in the form of stiffness of the knee joint. It may be due to the original nature of the injury or it too may be due to treatment. It will be mentioned later. The particular pitfalls that treatment must be designed to avoid are too little or—more important still—too much extension, loss of line and strain on the knee joint.

When a case is treated by continuous weight nd pulley traction, the pull of the weight is ansmitted through the tibia to the long thigh nuscles inserted into the tibial head. According to ie amount of weight applied, the shortened muscles tretch out and then assume a state of postural tone ;hich resists the pull. The greater the weight that ; applied, the greater is the stretch and the stronger he resistant tone (Fig. 1). The quadriceps, as the nain muscle of posture, probably plays a major ôle in striking an equilibrium with the weight. 'heoretically it should be possible to apply to any iarticular case that amount of weight which will naintain the correct amount of stretch. The :quilibrium must be an unstable one, however, as ι suspended weight possesses inertia and can ;enerate momentum, and any movement of the iatient must alter temporarily the forces in operation.)ver the course of two or three weeks the muscles vaste and tone presumably lessens, so that the weight should be correspondingly reduced to allow for this. Each case differs from the next in the reaction of the muscles and in the rapidity of wasting and of bone union. There is no mathematical formula for determining the exact amount of

FIG. 1.—Weight traction. Distal extension of muscles.

weight required at any particular time, and adjustments must be made on a purely empirical basis guided by frequent X-ray examination for position. These are not merely theoretical arguments. In practice it was found that in a proportion of cases satisfactory equilibrium could be achieved, and by judicious adjustments of the weights length and line could be preserved throughout the treatment. But in other cases treated similarly the behaviour was quite different.

Gnr. W. sustained a closed fracture of the femoral shaft among other injuries in an air raid. On 29th January 1942, after manipulation under an anæsthetic, twenty pounds weight was applied to a pin through the tibial

tubercle. The following day an X-ray showed good position and adjustment was not considered necessary. Five days later a further X-ray showed that the fracture was overpulled to the extent of half an inch, and the weight was accordingly reduced by half, to ten pounds. Two days later a third X-ray showed that not only had the gap closed but the fragments were over-riding by half an inch and there was lateral angulation of about twenty degrees. The weight was increased again to fifteen pounds and a fourth X-ray, six days later and fourteen days after the injury, showed that although the over-riding was now corrected, the lateral angulation persisted. Callus was faintly evident. Twenty pounds weight was attached once more and a pressure pad applied to the apex of the angle; but there was no change in the angulation after a further fourteen days, and a manipulation was necessary to straighten the limb. It has been remarked by Watson Jones that the correction of distraction often leads to angulation.

This case is not an isolated example. It represents a group of cases in which weight traction proved most difficult to control and led to the development of complications.

When weight traction is applied, the lower femoral fragment follows the tibia by virtue of the capsule of the knee joint. The only major muscle which is attached directly into it from a point above the fracture is the adductor magnus, and the tension in the knee joint ligaments is equivalent to the tone of this muscle and is relatively slight. When union has progressed sufficiently to fix the fractured surfaces and prevent movement in a longitudinal direction, no further traction is really necessary to maintain length. But unless a moderately strong pull is still applied the recovering medial muscles will angulate the bone. The transmission of the pull is now rather different. The lower fragment is anchored at the fracture and is no longer free to follow any further extension of the weakened muscles. Instead of being absorbed by the muscles, the pull passes from the tibia directly to the femur through the ligaments of the knee joint.
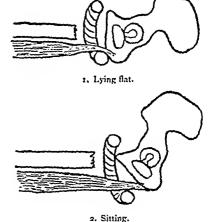
In the cases treated by weight traction in a Thomas splint with knee flexion piece, lateral angulation occurred with annoying regularity, and it often proved difficult to correct. According to the principle that any two sides of a triangle are longer than the third side, angulation necessarily implies some shortening, but in practice a moderate angle may produce so little actual difference in length that longitudinal traction cannot be entirely relied upon to prevent it, and will certainly not correct it unless an excessive pull is used. It was not so much during the early stages of treatment that the deformity asserted itself, as later on when weight was reduced in order to spare the knee. It is partly due to recovering muscular activity on the medial side and partly due to the position of the patient. With the hip and knee flexed the weight operates in the line of the femur at an angle of some forty-five degrees above the horizontal, and it expends part of its force against gravity. Reduction of the weight releases the action of gravity and the lower part of the limb slumps back into the splint and this promotes angulation.

. The splint itself may also play an important part in the encouragement of angulation. It is not always fully recognised that the Thomas splint was designed to bear on the ischial tuberosity, but can do so only when the patient lies flat with the hip extended. In this position the tuberosity forms the most distal prominence of the pelvis and the hamstrings are relaxed (Fig. 2). If the patient sits up, the tuberosity rotates backwards away from the ring and the hamstrings tighten across it. At the same time the pubic ramus swings down and forms the point on which the ring bears. Pressure on this region can rarely be tolerated and the patient eases the ring down the thigh. The pelvis and upper fragment are then released and tend to tilt inward across the inner side of the ring which forms a fulcrum in the adductor region. A pressure pad with a purchase on the side bar of the splint is the usual method of correcting angulation. But if a pressure pad is used in these circumstances it simply draws the ring of the splint laterally into the adductor muscles and increases the pressure of the fulcrum. It does little to correct the angle. A pressure pad is reliable only when the whole limb, including the pelvis, bears a constant fixed relationship to the splint. This is impossible with Braun's frame or with any system of slinging the leg on a suspended splint. It is effective if the method of fixation in a straight Thomas splint is used.

1. Lying flat.

2. Sitting.

FIG. 2.—Relation of ischial tubercle to ring.

Late angular deformity was also encountered in cases treated by fixed extension when enthusiasm for early movements led to too early release of the limb.

Sgt. O. had an oblique fracture of the middle of the shaft due to a bullet wound. He was treated with fixed skin extension and good reduction was obtained and held. After seven weeks his fracture seemed quite firm and the extension plasters were removed and leg raising exercises started. Three days later he had developed twenty-five degrees of lateral angulation which necessitated a further four weeks of extension with strong leverage over a fulcrum for its correction. The temptation to go too fast in the recovery stage must be resisted.

Rotational deformity consisting of an inward twist of the knee and leg is not an uncommon end result. It is often associated with some lateral angulation, and in the position of knee and hip flexion both these deformities are very difficult to detect on routine clinical inspection. The position of the limb tends to mask them and precludes accurate assessment by comparison with the sound leg. The inward

twist may be discovered only when the patient starts getting up and it is then too late. It is due to the action of the glutei and psoas which externally rotate the upper fragment in some cases. When this happens it is impossible to control the upper fragment, and correction must be obtained by positioning the lower limb in external rotation. It is not easy to assess whether this is required. The position of the greater trochanter may be palpated, and if it lies further back than the trochanter of the opposite femur, some degree of rotation may be assumed. If an X-ray taken during reduction shows that apposition is not good, a second film should be exposed with the knee and foot externally rotated about thirty degrees. This may show more accurate reduction and give a clue as to the correct position in which the limb must be immobilised. Rotational correction is possible only with the limb almost straight ; when the knee is flexed the leg can lie only in the antero-posterior plane.

The setting up of a fractured femur is not uncommonly treated as a minor procedure : perhaps an injection of morphia is given before applying skin extension, or a little pentothal or local anæsthetic for the insertion of a pin, and it is hoped that the weight will do the rest. Reduction can certainly be achieved by these means, but as the case of Gnr. W. shows, there is little time for gradual correction of deformities and a very close watch on the behaviour of the fracture is necessary. It is much simpler and much more reliable to carry out a definite manipulative reduction under full anæsthesia as the first stage in the treatment, to check the position by X-rays, and then to immobilise the limb in the splint. In two types of case such a manipulation is of prime importance : it is often possible to engage the ends of a transverse fracture, and if this is achieved, half the battle is won ; secondly, there is the occasional case in which the upper fragment penetrates the quadriceps muscle, and only by a strong pull and manipulation can it be freed.

In the casualties arriving at the Orthopædic Centre, difficulty in restoring full length was hardly ever experienced, even in the closed fractures. In fact, when there was much muscle damage from shell wounds, a moderate pull might distract the fragments only too easily. These patients had lain for a few days in Tobruk splints with their limbs immobilised and muscles extended, before they reached the base. When they came to definitive treatment, the absence of muscle spasm was a notable feature and the limb pulled out easily. In a fresh fracture treated immediately, full length may be impossible to obtain, especially if the subject is powerfully muscled and there is much swelling in the thigh. But if the limb is pulled out as far as possible and held in this position in a splint for four or five days, a second manipulation at the end of that time will almost always succeed.

Supposing now that the fracture has been reduced and the limb placed in a straight Thomas splint with the ring in contact with the ischial tuberosity and the leg below the fracture fixed to the lower end

of the splint, what forces are in operation on the limb ? This method of treatment is often referred to as " fixed traction," but the term is a misnomer. It arises from a conception of slow extension of the leg by repeated tightening of the cords. There is no traction operating in a direction away from the body ; the force should be envisaged as acting in the opposite direction (Fig. 3). The lower leg should be regarded as a fixed point in relation to the splint, and the thigh muscles, acting from their insertion to the head of the tibia, exert a pull on the pelvis in a downward direction and press the ischial tuberosity against the ring.

At first, when muscle tone is strongest, the pressure on the tuberosity may be heavy and cause complaint. It is relieved by raising the foot of the bed and allowing body weight to pull in an opposite direction to the tension in the muscles. The actual pressure on the tuberosity then amounts to the force exerted by the muscles minus the pull generated by body weight ; and provided that the latter is not the greater, the tuberosity remains in position and the mechanics in the limb itself are unaltered. Charnley has demonstrated that a nine-inch elevation of the foot of the bed produces in the case of a ten-stone subject a pull in the region of six pounds, and a twelve-inch elevation increases the pull to twelve pounds.

With such a method of fixation the side bars of the splint act as rigid props between the lower limb and the pelvis, and the fracture is immobilised in a longitudinal direction. There is no movement to cause spasm of the muscles. There is no constant stretching force to engender reactive contraction. The tension is due to the tone of a muscle at rest and is much less than that in a

Fig. 3.—Skeletal fixation to splint. No traction. Muscle tone acts on pelvis.

muscle continuously subjected to stretch from a suspended weight. It is found that the tension diminishes very rapidly after the first two or three days until by the end of the third week it is very slight. When voluntary contractions of the muscle return they act between the pelvis and the head of the tibia—two fixed points—and so have little tendency to produce angulation of the femur. Throughout the whole process the main muscles in operation work between these fixed points and bridge the knee joint. At no stage can there be any strain on the ligaments of the knee joint.

The method of fixed traction is criticised on the grounds that skin extension is unreliable and that the strapping always slips. The objection is perfectly valid. Skin extension was given a thorough trial and slid down the limb in every case, especially during the early stages when muscle resistance was maximal but when it was most

important to maintain reduction. Sores on the dorsum of the ankle and over the tendo Achilles were prevalent despite all precautions. Possibly excessive perspiration in a warm climate checked efficiency. But in all descriptions of treatment by this method the necessity for regular tightening of the tapes in order to take up the slack is stressed (Diggle, 1942). There seems to be little point in performing a careful reduction under anæsthesia and then using an apparatus which allows the tension to slacken off at intervals afterwards. It is a remarkable fact that the advocates of the principles of H. O. Thomas have retained his original methods of applying them virtually unchanged. Fixed traction seems to be wedded to skin extension for better or for worse, and a weight seems to be the inseparable companion of a skeletal pin. There is no need to use skin extension. A pin through the tibial tubercle can equally well be adapted to fixed traction as it is to weight traction, by attaching it with cords to the lower end of the splint, and it gives far greater precision of control than skin extension. At the same time it leaves the leg below the knee unencumbered with bandages and removes the risk of pressure sores. Minor skin infection at the pin holes was the worst complication encountered in a large number of cases so treated.

The most serious and troublesome complication of a fractured femur is stiffness of the knee joint. In the absence of any obvious traumatic cause, such as laceration of the quadriceps, or damage to the joint itself in the original injury, stiffness still results. The pin, originally introduced into the lower end of the femur close to the capsule, was rightly condemned. But its removal to the tibial tubercle far away from the joint has not made any marked difference. A healthy knee joint does not develop more than a transitory limitation of movement if it is immobilised in a position of rest. It does so if weight and pulley traction is applied to it for any length of time, and the degree and permanence of the stiffness seems to be proportional to the length of time the traction is in operation. Watson Jones postulates that a constant stretching force acting on a ligament may cause an irritative reaction in the joint which results in adhesion formation. This pathological sequence is well recognised in the foot where repeated strain of the plantar ligaments leads to adhesions in the mid tarsal joints. It has already been shown that weight traction pulls directly on the knee ligaments as soon as the bone ends are anchored longitudinally, and it is a fact that this traction can actually stretch the ligaments if it is continued after union has commenced.

Cpl. B. had a severely infected compound fracture with slow union, and was treated with weight and pulley traction in a Thomas splint with knee flexion piece. The direction of the pull was in the line of the femur. After two months in this apparatus there was anterior subluxation of the head of the tibia of almost half an inch which was easily visible on inspection, and was due to stretching of the anterior cruciate and collateral ligaments.

Two other cases were noted in which this subluxation was evident, and several cases were seen in which there was demonstrable laxity of the collateral ligaments and an apparently loose knee, but at the same time limitation of flexion. Much can be done during immobilisation to prevent the development of stiffness. Daily passive manipulations of the patella are useful, and quadriceps exercises at an early date are of the greatest value. Movements will return far more rapidly if the muscles are strong enough to produce them. Once more the position of the leg in the splint is of importance. With the knee flexed the quadriceps tendon is stretched and the patella falls into the intercondylar notch. It cannot be moved appreciably either in an up and down, or side to side direction. Quadriceps contractions are difficult to perform with the knee bent, and are nothing like so strong or complete as they are when the knee is extended. Extension of the muscles by a weight seems to prolong the inhibition of voluntary contractions which return at a much earlier stage when the limb is fixed.

Continuous skeletal traction was abandoned then, in favour of the method of reduction under anæsthesia followed by skeletal immobilisation in a straight Thomas splint. The term " fixed traction " is omitted as it implies a false conception of the mechanics. A Steinman's pin passed through the tibial tubercle and fastened to the lower end of the splint was used to obtain fixation of the lower fragment. The limb was put up with a pad under the fracture and lower fragment to correct posterior angulation and produce some fifteen degrees flexion at the knee joint, and a lateral pad was applied to the site of the fracture and in some cases was reinforced with a pad against the medial femoral condyle. A cuff of plaster of Paris applied round the splint and limb and moulded in at the sides in the same way as in the Tobruk splint, and then cut away in front to leave a lateral and medial buttress, serves very well.

Perhaps the most striking feature which resulted from this change of policy was the ease of management of the cases in the wards. Constant checking of position by X-ray examination was no longer necessary. Provided that the line of the limb looks straight, the ischial tuberosity is in contact with the ring and the length of the limb by measurement is correct, nothing can be wrong. The foot of the bed, at first raised nine or twelve inches, can be gradually lowered as tension slackens. After the first few days a physiotherapist supervises daily active exercises of the foot, ankle and quadriceps, and carries out passive manipulations of the patella. As soon as the leg can be raised from the splint—about the fifth or sixth week in a straightforward case—the cords may be released for a short period each day and gentle flexion and extension exercises cautiously started under supervision. The apparatus should be carefully replaced afterwards. When the callus is no longer tender and lateral stress on the bone does not cause pain, the patient is ready for a weight-bearing caliper.

Unfortunately it was impossible to follow cases through to their conclusion and to obtain details of the functional end results. As soon as a man reached the convalescent stage he was evacuated to South Africa. However, the interim progress was noted in two small groups of comparable battle casualties, mostly with compound fractures. In the first group, treated by weight and pulley traction, the average length of time between wounding and reaching the stage of being up in a caliper and fit to move on, was eighteen weeks. In the second group, treated by the method outlined, the time was reduced to twelve weeks. One half of the latter group had by that time recovered eighty degrees or more of knee flexion.

Throughout this discussion two main themes run. The first concerns continuous weight traction. It has been publicly suspect (Girdlestone, 1943) for some time as a potentially harmful method of treatment. Theoretically it is illogical on both mechanical and physiological grounds. In practice it was found to be difficult of management, unreliable in result and even conducive to complications, to the prevention of which treatment should be directed. The second concerns the position of the limb. Flexion of knee and hip leads to many difficulties in the estimation and correction of deformity and does not favour rapid recovery of function. In the majority of cases the original Thomas splint, unadorned with any modification or attachment, is still the best available apparatus for the treatment of these fractures.

Smillie has classified fractures of the femoral shaft as the " Cinderellas of the surgical wards," since the introduction of the Smith Petersen nail promoted femoral neck fractures from that unenviable position. Perhaps if the method of continuous weight traction were finally discarded even these cases might lose some of that unattractiveness which renders them so much less desirable than their ugly sisters.

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A DIETARY SURVEY OF PREGNANT WOMEN AND SCHOOL CHILDREN IN EDINBURGH

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A SURVEY of hæmoglobin levels made in Edinburgh in 1942 (Davidson *et al.*, 1942, 1943) showed that while in most of the groups studied the levels were satisfactory, an exception occurred in the case of pregnant women and school children who exhibited a considerable incidence of anæmia. It was therefore considered of interest to investigate the diets of these two groups, in order to see whether there was any indication of a dietary deficiency, which might have been responsible for the anæmia.

Shortly after the start of the study in 1944, a repeat investigation of the hæmoglobin levels was made (Davidson *et al.*, 1944), and it was then found that the incidence of anæmia was much less. It did not therefore seem probable that any marked dietary deficiency would be apparent. But it was felt that it was still possible to discover whether the intake of some nutrients lay on the borderline of deficiency and whether these intakes would have been materially affected by the known changes in the Nation's diet between 1942 and 1944.

The diets were studied by the individual method. The food, as eaten, was weighed and recorded for a week by the women or the children's mothers. With preliminary explanation and some supervision, results which appeared to be reliable were obtained in the majority of cases. Any that were felt to be unsatisfactory were discarded. From the records of the food intake the week's consumption of nutrients was calculated with food tables. The accuracy of this method has been studied by Widdowson and McCance, and its advantages, together with those of other available methods, have been thoroughly dealt with by these authors (1945). The method is only possible with reliable women who will take some trouble with weighing and recording, and the subjects investigated were, therefore, not a random sample, but a group of the more intelligent and better off.

The 35 expectant mothers were all from two districts on the outskirts of Edinburgh, consisting mainly of new Corporation houses. Their names were obtained through the co-operation of Dr Finlay of the Department of Public Health. The husbands of 23 were in the Forces and those of the other 12 were skilled artisans. Seventeen of the women were living with their own or their husband's people. The women were seen in the later months of pregnancy, when it was possible for them to have obtained their priority rations. The survey was carried out between February and September 1945.

The 52 school children were from a school in a poor district in the

centre of the town and from a school in a new housing district on the outskirts. No difference in diet between the two districts was apparent. Fifteen of the children had school dinners five days in the week of investigation. Their ages varied from 7-12 years. The survey lasted from February 1944 to February 1945.

FOODSTUFFS EATEN

Rationed.—In Table I the consumption of rationed foods is summarised. No direct investigation of whether the full ration was

TABLE I

Weekly Amounts of Rationed Foodstuffs eaten by Pregnant Women and School Children

| Food. | Pregnant Women. | | | School Children. | | | | |
| | | | | Dinners at Home. | | | School Dinners. | |
	Ration oz.	Range and Mean, oz.	Nos.* out of 35.	Ration oz.	Range and Mean, oz.	Nos.* out of 37.	Range and Mean, oz.	Nos.* out of 15.
Meat . . .	15	3-32 18·2	12	10	4½-26 11·8	14 (1)	2-12 5·5	14
Bacon . . .	1½-2	1-12 4·4	4 (1)	2	½-6 3·0	14 (7)	2-4 2·6	5 (4)
Cheese . . .	2	½-6 1·7	26 (16)	2·4	1-4 2·5	12 (3)	1-4 2·2	8 (5)
Eggs, fresh and dried .	18	2-19 6·9	32 (1)	6	1-16 5·8	20 (9)	2-14 6·2	6 (2)
Milk † . . .	140	15-204 79·5	31	70	30-159 82·5	15	11-106 65·1	10
Butter and margarine .	6	1-21 7·1	12	6	1-27 9·3	13	3-16 8·1	3
Sugar and jam . .	12	½-26 12·3	16	12	3-23 11·5	20	6-18 11·2	7
Sweets . . .	3	1-22 5·4	24 (18)	3	1-11 3·7	2	1-8 3·7	1
Orange juice . .	3½	...	(15)	...	...	...	...	...
Cod-liver oil . .	...	...	(23)	...	...	...	...	...
School milk . .	...	...	...	33	...	(1)	...	(0)

* Numbers eating less than the ration and in parenthesis numbers not eating any. The ranges and means are for those eating these foods.
† Liquid oz. school milk not included.

bought was made. This can only be inferred from the amounts eaten in the week of the survey. The method is not without errors. In the case of meat, since the amount of the ration varies inversely with the price, a small consumption may only mean that an expensive cut was bought. In the case of dry goods, the consumption may have varied considerably from week to week. These two errors, due to weekly variations, are probably to some extent eliminated when the mean intakes for the groups are considered. Again, in the case of foods which were cooked, it is uncertain what weight was lost in cooking, and arbitrary figures have had to be adopted. It has been assumed that 1s. 2d. worth of uncooked meat provided an average

of 10 oz. of cooked meat and that 4 oz. of bacon was reduced to 2 oz. after cooking.

The following points may be commented on. The mean consumption of meat by the women and home-dinner children was satisfactory, though a high proportion did not apparently eat the whole ration in the week of the survey. The cheese and dried-egg rations were poorly taken up by all groups. The women did not make full use of their extra milk ration, although this was obtainable at a cheap

TABLE II

Weekly Amounts of Various Unrationed or Pointed Foodstuffs eaten by Pregnant Women and School Children

Food.	Pregnant Women. (35).		School Children.			
			Dinners at Home. (37).		School Dinners. (15).	
	Range and Mean, oz.	No. taking.	Range and Mean, oz.	No. taking.	Range and Mean, oz.	No. taking.
Animal protein foods—						
Tinned, on points	1·10 / 4	17	1·6 / 3	25	2·6 / 3	7
Fish	1·16 / 9	29	2·10 / 4·5	23	4·5 / 5	3
Offal	2·32 / 10	9	1·15 / 5	11	4·10 / 7	2
Sausages	2·16 / 8	27	1·17 / 6	27	1·8 / 4	13
Bread, tea bread and cake	19·108 / 62	35	17·136 / 70	37	37·99 / 69	15
Potatoes, total	11·107 / 45	35	2·63 / 36	37	7·63 / 25	15
Chips	2·45 / 14	33	2·35 / 12	30	3·27 / 12	12
Vegetables, total	3·35 / 12	34	3·21 / 11	34	3·12 / 6	12
Uncooked	...	16	...	9	...	3
Porridge	6·96 / 31	19	6·87 / 32	28	3·63 / 31	10
Soup	7·98 / 28	32	8·104 / 29	36	4·36 / 20	7

Ranges and means are for those taking these foods.

rate. Only 4 out of the 35 drank a pint a day. Only 20 were taking orange juice and only 12 cod-liver oil. The children having school dinners ate half as much meat and less milk than those having home dinners. School milk was drunk by all except one child.

Unrationed Foods and Foods on Points.—The consumption of some important groups is summarised in Table II. At the time of the survey of the women's diets, fish was much easier to get than when the children's diets were studied. It should be noted that the consumption of potatoes and vegetables by the school-dinner children was less than that of the home-dinner children, but that in other respects their intakes were very similar. The high consumption of

sausages and chipped potatoes is of interest. Figures for porridge and soup are included as these foods are widely eaten in Scotland.

THE AMOUNTS OF NUTRIENTS CONSUMED

The calories, protein, fat and iron contents of the foods eaten were taken in most cases from the figures of McCance and Widdowson (1940). A few values were taken from the Medical Research Council memorandum on the Nutritive Value of War Time Foods (1945). The figures used for ascorbic acid in foods were those given by Olliver (1943). Fried potatoes were assumed to have the same ascorbic acid value as boiled potatoes.

TABLE III

The Daily Intake of Calories, Protein, Fat and Iron by 35 Pregnant Women and 37 School Children, and the Suggested Requirements of these Nutrients

| | | Protein, g. | | Fat, g. | Iron, mg. | | |
| | Calories. | | | | Extraction of Flour. | | |
		Total.	Animal.		85 Per Cent.	80 Per Cent.	70 Per Cent.
Pregnant women—							
Minimum	1660	44	16	64	7·9	6·3	5·5
Maximum	3650	133	85	153	24·2	22·0	17·5
Mean	2550	91	49	96	15·0	13·2	12·4
Suggested requirement	2500	85	40	100	...	15·0	...
Number with less	(15)	(16)	(9)	(21)	(20)	(26)	(27)
School children—							
Minimum	1730	57	21	58	10·4	7·9	6·6
Maximum	3700	127	61	158	23·3	20·6	19·3
All ages, mean	2645	83	40	102	14·5	12·5	11·5
7–9 years, mean	2570	81	39	99	14·3	11·9	11·0
Suggested requirement	2000	60	40	100	...	10·0	...
Number with less	(3)	(2)	(11)	(13)	(0)	(5)	(9)
10–12 years, mean	2800	88	41	106	15·7	13·7	12·6
Suggested requirement	2500	70	40	100	...	12·0	...
Number with less	(2)	(2)	(3)	(4)	(0)	(4)	(5)

The intakes of each nutrient have been compared with the amounts, which it has been suggested, that pregnant women and children require. The suggested amounts of calories, protein and iron are those given by the National Research Council. Those taken for animal protein and fat are not established criteria, but amounts which it has been thought are needed if the diet is to be palatable. The figures taken for ascorbic acid are half those given by the National Research Council, since there is abundant evidence that those standards are too high.

In Table III the range and mean intakes of calories, protein, fat and iron are shown. Three sets of figures are given for iron, representing the intake when the bread was made from flour of 85 per cent., 80 per cent. or 70 per cent. extraction. At the time of the women's survey the flour was of 80 per cent. extraction, while at the time of the children's survey it was of 85 per cent. extraction.

The mean consumption by women and children of calories, protein, animal protein and fat was as high or higher than the suggested requirements. The mean iron intake of the women was slightly less than the suggested requirement, but that of the children was adequate. The range of intake of these nutrients by both women and children was large. In the case of the children this variation was to some extent due to age. This is shown in Table III, where the mean intakes for children of 7-9 are compared with those of children of 10-12. The effect of age was, however, inconstant. Some children of 7 ate more than some of those of 12.

The amounts of protein, fat and carbohydrate eaten by the women and children varied with the caloric intake. This is shown in Table IV,

TABLE IV

The Proportions of Calories Supplied by Protein, Fat, Carbohydrate and Bread at Different Levels of Caloric Intake

	Daily Calorie Intake.					Suggested Proportions.
	1500+	2000+	2500+	3000+	Mean.	
Pregnant women—						
Number in each group	(6)	(9)	(14)	(6)	(35)	...
Mean calorie intake	1750	2200	2700	3500	2550	...
Per cent. from protein	14	15	14	14	14	...
Per cent. from fat	37	38	33	33	35	25
Per cent. from carbohydrate	49	47	53	53	51	...
Per cent. from bread	25	22	27	24	25	...
School children—						
Number in each group	(5)	(12)	(9)	(11)	(37)	...
Mean calorie intake	1860	2280	2700	3350	2645	...
Per cent. from protein	14	13	13	12	13	15
Per cent. from fat	34	35	36	35	35	25
Per cent. from carbohydrate	52	52	51	53	52	...
Per cent. from bread	22	24	25	32	26	...

where the proportion of calories derived from these nutrients at different levels of calories intake is shown. On the whole the proportions were the same for women and children and remained constant at all levels. Minor exceptions were that the women with high calorie intakes got fewer calories from fat and more from carbohydrate and that the children with high calorie intakes got less from protein and more from fat and carbohydrate. The proportion of calories from bread is also shown in Table IV. This remained very constant for the women, but rose steadily with increasing calorie intake in the case of the children. From these findings it followed that when the calorie intake fell below about 2500 a day, the amount of protein tended to be below 85 g. Fifteen women fell into this group. When the calorie intake was below 2000 a day the protein intake tended to be below 65 g. Five children fell into this group. The fat intake was generally under 100 g. when less than 2500 calories daily were being eaten. The iron intake also varied with the calorie intake. But

in the case of the children, even those with the smallest intakes of calories obtained 10 mg. a day. In the case of the women, however, only when the calorie intake was 2500 or more was the iron intake 15 mg. daily.

The ascorbic acid intakes are shown in Table V. The women and children who took oranges or orange juice are shown separately. There was a marked difference in consumption at different times of the year, this being due to a large extent to the seasonal change in the ascorbic acid in potatoes. In the summer most of the women obtained 50 mg. a day, but few got this amount in the winter and spring, even when taking orange juice. The amount of orange juice recommended by the Ministry of Food supplies 22·5 mg. of ascorbic acid daily.

TABLE V

The Mean Daily Intakes of Ascorbic Acid by 35 Pregnant Women and 37 School Children

	January-June.			July-December.			Whole Year.[*]	
	Total mg.		From Potatoes mg.	Total mg.		From Potatoes mg.	Total mg.	
	No Oranges.	Oranges or Orange Juice.		No Oranges.	Oranges or Orange Juice.		No Oranges.	Oranges or Orange Juice.
Pregnant women	14	43	6	60	81	40	29	56
Number	(11)	(13)	(24)	(4)	(7)	(11)	(15)	(20)
Number with less than 50 mg. .	(11)	(10)	...	(2)	(0)	...	(13)	(10)
School children .	15	62	5	33	44	19	26	53
Number	(12)	(9)	(21)	(14)	(2)	(16)	(26)	(11)
Number with less than 30 mg. .	(12)	(1)	...	(6)	(0)	...	(18)	(1)

[*] Calculated as though there had been equal numbers in each quarter.

Approximately half the children seen in the summer and autumn obtained 30 mg. of ascorbic acid daily, but in the winter only with oranges was this amount obtained.

CHILDREN WITH SCHOOL DINNERS

The total nutrient intake of these 15 children is not known, as the amounts they ate at school were not measured. Their home consumption is shown in Table VI, where it is compared with that of the 37 children with all meals at home. Their mean intake was lower by 495 calories, 21 g. protein, 22 g. fat, 2·2 mg. iron and 12 mg. ascorbic acid. In the same table are given the mean composition of three sets of Edinburgh school dinners. These figures were obtained by analysis and have been kindly supplied by Dr C. P. Stewart. The size of the meals varied considerably, but in the case of the smaller ones second helpings were available. The meals supplied ample calories and if portions such as these were eaten by the children investigated, their caloric intakes would have been considerably higher

than those of the home-dinner children and their intakes of protein, fat and iron equal to or greater than the intakes of the home-dinner children. However, it seems improbable that such large amounts were eaten. In parenthesis in the table are shown the amounts of nutrients which 500 calorie portions of similar composition would have contained. The amounts of protein and fat were less than those needed to bring the intakes of the school-dinner children up to those of the home-dinner children. When ascorbic acid is considered it is seen that even if full portions had been eaten the school-dinner children would have obtained less than the home-dinner children.

TABLE VI

Mean Daily Amounts of Calories, Protein, Fat, Iron and Ascorbic Acid eaten by Children at Home, (1) when having all Meals at Home, (2) when having School Dinners, and the Amounts of these Nutrients provided by some School Dinners (3)

	Calories.	Protein, g.	Fat, g.	Iron, mg.	Ascorbic Acid, mg.
Home intakes—					
(1) 37 children with all meals at home . .	2645	83	102	14·5	26
(2) 15 children with school dinners . . .	2150	62	80	12·3	14
Difference (1)-(2) . .	495	21	22	2·2	12
(3) *School dinners—*					
7 in March 1943 . .	620 (500)	16 (13)	19 (15)	5·6 (4·5)	7 (6)
3 in September 1944— Centre 1 . . .	860 (500)	22 (13)	33 (19)	...	} 10 (6)
3 in September 1944— Centre 2 . . .	1020 (500)	35 (17)	39 (19)	...	

In parenthesis are shown the amounts of nutrients provided by portions of the school dinners giving 500 calories.

DISCUSSION

It is clear from these surveys that it was possible in 1944 and 1945 for both expectant mothers and school children to obtain a diet which supplied adequate amounts of calories, protein, fat and iron. A considerable number in both groups had higher intakes of these nutrients than are considered necessary. This suggests that little difficulty was experienced in finding a good diet when the rations and priorities were used and unrationed foods were bought intelligently. It is worth mentioning that rationing has probably improved the nutrient value of diets such as these by limiting the sugar intake. Before rationing very large amounts of sugar were used and would have replaced appreciable amounts of protective foods.

At the same time it appears that while few of the children obtained less calories, protein or iron than the suggested requirements, a high proportion of the women obtained considerably less. This may have been due to small calorie needs and so to a low consumption of all

foods, but it appears more probable that the unpalatability of diets containing little protein or fat resulted in a low intake of all foods. This consideration would not bear so much weight with children who are in general less particular about their food and are willing to fill up with bread. If this is so, it is necessary to see why the protein and fat consumption of some women was so low. It is at once apparent that the chief cause was the failure of these women to make use of their cheese ration and their priority rations of milk and dried eggs. Had these been used there would have been a higher intake of both protein and fat. In each case, custom was against a larger consumption. Cheese is not eaten freely in this part of the British Isles, dried egg is still a new and relatively unappreciated food and milk has been considered too expensive to use except in tea. It therefore appears that in order to improve the diet, education, rather than the supply of other foodstuffs, is necessary.

It is difficult to judge whether the ascorbic acid intakes were satisfactory, since no satisfactory standards have been established. But the very small amounts eaten, especially in the winter and spring, suggest that a more general use of vegetables and the priority orange juice is very desirable.

While the children having all meals at home obtained in most cases adequate amounts of the nutrients investigated, the school-dinner children had, at home, appreciably lower intakes of protein, fat and ascorbic acid. This was due to the fact that the school dinners were in nearly every case considered as a substitute for, not as a supplement to, a cooked dinner at home. The mean consumptions of rationed meat and vegetables by these children were half those of the others, and in addition they drank less milk. The school dinners were not rich in protein and ascorbic acid, so that it appears probable that the children taking them had low intakes of these nutrients. This suggests that a meal of the nature of an Oslo breakfast, rich in protein and vitamins, would be a more valuable addition to the children's diets than the high caloric meals provided here.

The chief changes in the foods available for pregnant women between 1942 and 1944 were the change in the extraction of flour from 70 per cent. to 85 per cent., the introduction of orange juice and cod-liver oil in December 1942 and of an extra half-ration of meat and half-packet of dried eggs per week in July 1943. A pint of milk daily at a cheap rate had been available since July 1940. The difference in the extraction of the flour would, in the women here investigated, have made a mean difference in the iron intake of 2·6 mg. daily and considerably influenced the number of women getting less than 15 mg. daily. This change may have been one reason for the alteration in the incidence of anæmia. It is tempting to ascribe the reduction in the incidence of anæmia in 1944 to the introduction of extra meat and consequent improvement in the protein intake, especially as it appears that nearly all women took advantage of this priority and that even with this the protein intake was in many cases low. But the improve-

ment in the hæmoglobin levels of the women was apparent early in pregnancy, before the priorities had been obtained, so they cannot have been instrumental. The same applies to the change in ascorbic acid intakes. While the fall in the incidence of anæmia cannot, thus, be attributed to the introduction of priorities, it is clear from the results of this study how valuable the priorities for expectant mothers are.

The change in the extraction of the flour would have affected the children's diets rather more than the women's. If the bread had been white, the children investigated would have obtained a mean of 3·0 mg. less iron a day and a considerable proportion would not have got the 0·12 mg., which it is suggested that they need. A further change which had occurred in these two years was that the drinking of school milk had become much more universal. When one-third of a pint is taken five days a week it supplies 4·5 g. of protein a day over the whole week. If they had not had this, a number of the children would have had low protein intakes.

The high intakes of calories, protein and fat by the children suggests that it is not a reliable practice to consider that children of seven to twelve eat less than adults. Their food consumption would appear in many cases to be equal to that of a moderately active man or woman. Yet when dietary studies are made by observation of a household's consumption, the children are generally considered to eat less than an adult.

SUMMARY

The diets of 35 pregnant women and 52 school children were studied by the individual method in 1944 and 1945. The diets of many of the women were deficient in protein and iron, the former deficiency being due to a failure to make use of the rations. The children's diets were satisfactory in the majority of cases, but when school dinners were taken these were considered as substitutes for a cooked meal at home, and the 15 children taking them had less protein and ascorbic acid at home than the others. This lack was probably not made good by the school meals. The changes in the diet of expectant mothers and school children between 1942 and 1944 are discussed.

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CARBOHYDRATE METABOLISM IN OBESITY

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OBESITY is nowadays attributed to overfeeding and subsequent conversion of the caloric surplus into fat. This surplus—according to Newburgh and others (Newburgh, 1942)—may arise either from the ingestion of excessive food or the reduction of energy output. One or other of these factors can be recognised in the majority of obese subjects, but occasional cases fail to show either factor, even after an exhaustive examination. These subjects are usually unable to reduce their weight by severe dieting, and an increase of their metabolism by artificial means also effects very little reduction, and then mostly at the expense of tissues other than fat (Bauer, 1941 ; 1943 ; Rony, 1940). Obesity, in other words, must sometimes be due to the factors other than overfeeding. With a view to determining those factors, fifty-one unselected obese subjects and five normal cases as a control were subjected to the following investigations.

METHODS

(1) *Dextrose Tolerance Test* (*D.T.T.*).—This consisted in the administration of 50 gm. of dextrose in 300 c.c. of water, per 70 kg. of body weight, *i.e.* 0·7 gm. of dextrose per kilo, by mouth immediately after the taking of a fasting blood specimen.

(2) *Dextrose Insulin Tolerance Test* (*D.I.T.T.*).—This was carried out next morning in the same way, with the additional administration of 10 units of normal insulin per 70 kg. of body weight, *i.e.* 0·15 unit of insulin per kilo, intravenously after the taking of the fasting sample of blood.

Blood sugar was examined from the capillary blood by the Hagedorn-Jensen method. The samples were taken five times in four hours after ingestion of dextrose. Patients during this time were seated or in bed. The urinary sugar was determined by Nylander reaction before first and after the last blood sample. For three days before the tests the patients were kept on the animal protein-free diet without excess of carbohydrate or fat in order to avoid their influence on the post-absorptive utilisation of dextrose (Himsworth, 1933-34, 1935-36; Sweeney, 1927), but in sufficient amount to cover the energy requirement.
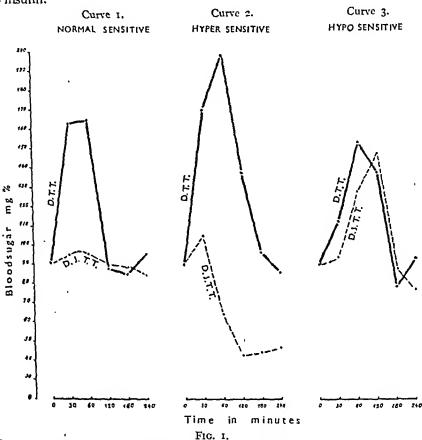
(3) Observation of *hypoglycæmic reactions* during both of the above tests.

(4) Observation of clinical symptoms of *hormonal disturbances*.

RESULTS

(1) NORMAL SUBJECTS.—Each of five normal persons subjected to the above investigations showed a response of the type seen in

Curve 1 of Fig. 1, in which D.I.T.T. yields figures much lower than those of the D.T.T., so that in the course of four hours of the test the blood sugar values fluctuate about the initial fasting blood sugar level. The lowest and highest values do not exceed 60 mg. and 120 mg. per cent. respectively. This type of curve represents normal senstivity to insulin.

Curve 1.
NORMAL SENSITIVE

Curve 2.
HYPER SENSITIVE

Curve 3.
HYPO SENSITIVE

Time in minutes

FIG. 1.
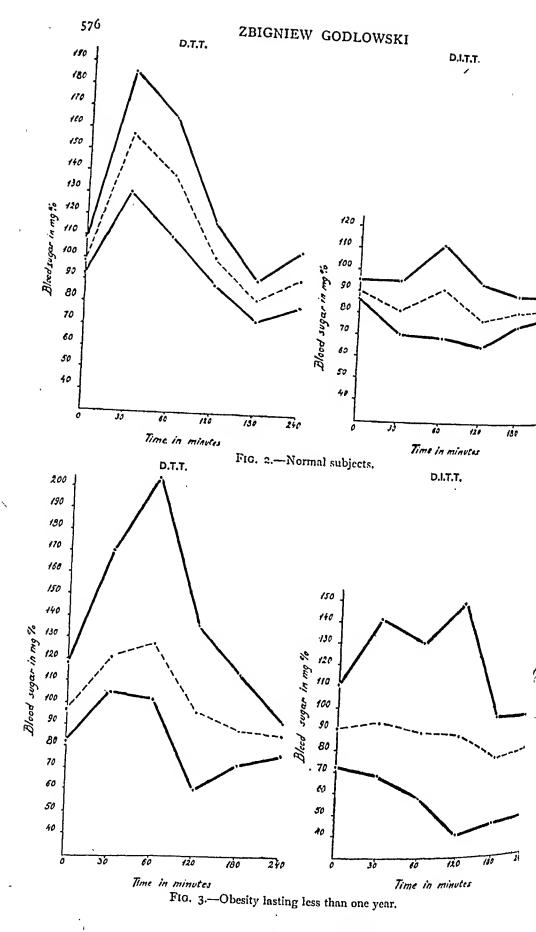
For the sake of convenience each of the curves has been constructed to start from 90, although they originally showed some variation.

Normal sensitive refers to case No. 1, Table 1.

Hypersensitive refers to case No. 1, Table 2.

Hyposensitive refers to case No. 11, Table 2.

(2) OBESE SUBJECTS.—Fifty-one such cases subjected to the same tests yielded information which should be interpreted from the point of view (*a*) sensitivity to insulin ; (*b*) duration of obesity ; (*c*) hypoglycæmic symptoms ; (*d*) hormonal disturbances.

(*a*) *Insulin Sensitivity in D.I.T.T.*—All cases irrespective of duration of obesity show one of three types of sensitivity :—

(i) *Normal Sensitivity to Insulin (Fig. 1, Curve 1).*—This type, as described under (1), occurred in 34 cases out of 51 or in 67 per cent.

FIG. 2.—Normal subjects.

FIG. 3.—Obesity lasting less than one year.

(ii) *Hypersentivity (Hr.) to Insulin (Fig. 1, Curve 2).*—This type was characterised by blood sugar values in D.I.T.T. of beyond 60 mg. per cent. and D.T.T. of normal range. It was found in 12 cases or 24 per cent.

(iii) *Hyposensitivity (Ho.) to Insulin (Fig. 1, Curve 3).*—This type involved blood sugar readings of approximately the same value in both D.I.T.T. and D.T.T. and was shown by five subjects or 10 per cent.

TABLE I

Normal Subjects

No.	D.T.T. 0' 30' 60' 120' 180' 240'	Hypoglycaemic Symptoms.	D.I.T.T. 0' 30' 60' 120' 180' 240'	Hypoglycaemic Symptoms.	Endocrine Symptoms.
1	109 183 163 115 73 97	+	92 70 102 81 77 72	o	none
2	100 159 118 88 91 105	+	95 84 69 65 79 89	++	,,
3	93 161 165 88 86 95	o	91 95 95 91 89 85	o	,,
4	93 130 110 89 80 84	o	89 89 112 94 88 87	o	,,
5	96 152 136 82 80 88	+	86 70 77 75 79 82	o	,,
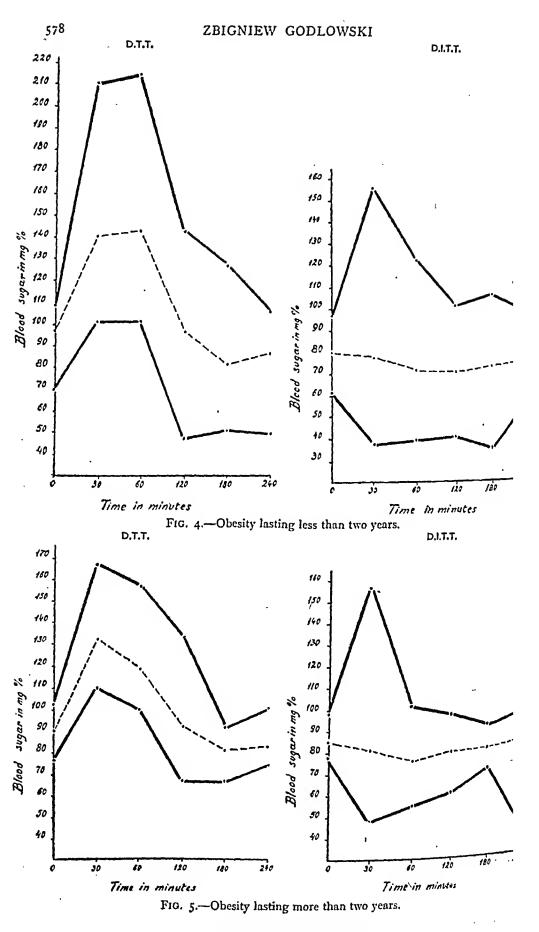
TABLE II

Obesity Lasting Less than One Year

No.	D.T.T. 0' 30' 60' 120' 180' 240'	Hypoglycaemic Symptoms.	D.I.T.T. 0' 30' 60' 120' 180' 240'	Hypoglycaemic Symptoms.	Endocrine Symptoms.
1	118 170 199 129 95 80	o	90 106 65 40 45 42 (Hr.)	o	gonadal— pituitary——
2	100 130 128 164 98 90	o	90 141 130 78 64 72 (Ho.)	+++	gonadal— thyroid——
3	86 166 143 60 80 91	o	92 108 95 52 85 91 (Hr.)	+	gonadal—
4	82 125 118 82 82 82	+++	98 93 92 91 95 95	+	epilepsy
5	91 105 116 127 114 93	+++	80 72 80 84 78 72	+++	suprarenal++
6	117 117 110 96 90 89	o	110 75 79 86 89 95	o	thyroid——
7	103 116 128 119 72 82	+	72 68 72 75 75 78	++	none
8	86 113 102 84 78 91	o	88 70 58 61 67 80 (Ho.)	+++	gonadal—
9	86 140 125 118 100 87	o	93 94 90 97 90 90	+	none
10	90 122 104 82 91 81	o	81 111 77 82 79 85	o	pituitary—"
11	82 112 152 136 78 93	+	88 93 129 149 88 75 (Ho.)	+++	gonadal—
12	82 136 125 74 75 77	o	82 79 100 82 86 89	+	pituitary—

(b) *Duration of Obesity* :—

(i) *D.T.T.*—The results of this test revealed a gradual deterioration in carbohydrate tolerance, although the latter still remained within normal limits.

(ii) *D.I.T.T.*—The results of this test were not conspicuously influenced by the duration of obesity.

(iii) *Insulin Sensitivity and Duration of Obesity.*—Hypersensitive and hyposensitive cases are distributed throughout all three groups more or less equally, but with the majority in the group of normal sensitivity. No relationship, therefore, exists between sensitivity to insulin and duration of obesity.

FIG. 4.—Obesity lasting less than two years.

FIG. 5.—Obesity lasting more than two years.

(c) *Hypoglycæmic symptoms* did not always correspond with the blood sugar values. Low glycæmia without hypoglycæmic symptoms

TABLE III
Obesity Lasting Less than Two Years

No.	D.T.T.	Hypogly-cæmic Symptoms.	D.I.T.T.	Hypogly-cæmic Symptoms.	Endocrine Symptoms.
	0' 30' 60' 120' 180' 240'		0' 30' 60' 120' 180' 240'		
1	89 140 118 84 72 80	o	90 154 102 92 72 64 (Ho.)	o	gonadal++ suprarenal++
2	88 125 116 67 77 82	+·	79 77 66 65 79 81	+++	gonadal---
3	102 116 105 95 93 101	o	98 96 53 80 92 97 (Hr.)	o	none
4	100 167 157 134 96 81	o	94 92 91 86 89 96	o	thyroid+ gonadal-
5	94 120 100 97 88 94	o	90 56 69 81 91 98 (Hr.)	+++	gonadal-
6	92 128 100 77 80 80	+	84 48 66 66 78 78 (Hr.)	+++	gonadal- suprarenal++
7	77 126 108 106 67 75	+	86 91 82 83 85 86	o	none
8	82 140 127 117 75 82	+	78 66 61 70 75 82	o	"

TABLE IV
Obesity Lasting More than Two Years

No.	D.T.T.	Hypogly-cæmic Symptoms.	D.I.T.T.	Hypogly-cæmic Symptoms.	Endocrine Symptoms.
1	92 116 132 119 127 106	o	90 110 114 110 110 117 (Ho.)	o	pituitary---
2	88 143 140 111 95 65	o	86 166 133 112 82 68 (Ho.)	o	thyroid--
3	82 135 148 48 52 50	o	72 93 110 79 72 65	o	gonadal-
4	98 204 160 85 83 78	o	96 102 93 57 45 42 (Hr.)	o	gonadal---
5	99 127 164 194 75 65	+	90 78 101 111 82 78	+	thyroid++
6	107 211 215 143 73 73	+++	107 94 84 82 86 94	o	gonadal---
7	77 102 116 86 76 74	++	91 100 96 95 91 89	o	none
8	86 158 133 102 63 76	+	93 91 93 74 74 89	o	"
9	87 118 105 87 87 96	+	88 58 58 51 67 83 (Hr.)	++	gonadal--
10	93 115 105 105 90 87	o	93 48 109 87 87 87 (Hr.)	+	pruritus
11	75 128 113 68 73 73	o	75 70 70 70 73 80	o	none
12	80 146 136 82 71 73	+++	72 86 84 59 68 68 (Hr.)	o	thyroid-
13	86 161 151 120 73 79	o	90 114 123 76 81 85	o	gonadal+
14	86 135 176 108 81 83	o	84 84 84 72 76 83	o	gonadal---
15	90 180 149 93 86 91	+++	88 78 65 92 92 95	+	gonadal++
16	74 121 102 84 74 74	+	76 65 49 — — — (Hr.)	+++	gonadal--
17	109 156 167 143 104 93	o	104 95 95 78 98 100	+	gonadal++ suprarenal+
18	97 130 122 100 89 96	+	95 91 107 91 94 96	++	suprarenal+ thyroid+
19	91 154 149 109 77 84	++	91 82 63 69 88 89	+	gonadal--
20	93 159 156 93 93 91	o	102 102 118 99 99 100	o	gonadal--
21	100 127 145 116 79 89	o	98 86 81 81 81 86	o	none
22	91 145 111 86 86 81	+	96 74 77 82 82 84	o	"
23	105 150 154 114 98 109	o	102 79 105 89 89 82	o	"
24	84 131 123 89 70 70	o	87 91 85 74 71 70	o	gonadal-
25	91 122 129 85 81 86	o	95 88 114 84 86 79	++	gonadal++ thyroid+
26	91 134 143 88 74 91	+	89 81 79 60 76 89 (Hr.)	+	none
27	89 138 120 120 86 98	+·	86 93 104 89 81 89	o	"
28	100 127 129 88 91 100	o	84 88 96 89 89 95	o	thyroid+
29	105 127 172 140 86 95	o	102 86 86 74 88 89	+	thyroid- gonadal-
30	84 145 129 114 84 82	o	84 74 84 81 77 93	o	thyroid++
31	95 158 161 112 82 89	o	96 93 91 81 91 104	o	gonadal- thyroid-

D.T.T.: Dextrose Tolerance Test. D.I.T.T.: Dextrose Insulin Tolerance Test.
Endocrine Symptoms.—Thyroid+ : B.M.R. more than 15 per cent.
    thyroid— : B.M.R. less than 15 per cent.
    pituitary— : thirst, striation, dystrophia adip.-gen., etc.
    gonads+ : menstrual disorder, genital organ hypertrophy, hypersexalism.
    gonads— : hypo-amenorrhœa, sterility, impotency.
    suprarenal+ : hypertrichosis, hyperpigmentation, etc.

occurred in cases No. 1, Table II and No. 4, Table IV. Such symptoms, on the other hand, were pronounced in association with normal or

even abnormally high blood sugar values as in cases No. 4, 5, 11 of Table II and No.'6, 7, 12, 15, 19 of Table IV. These results indicate that symptoms suggesting hypoglycæmia must sometimes be due to factors other than low blood sugar.

(d) *Hormonal disturbances* were identified as (1) *gonadal* in females from the occurrence of dysmenorrhœa, amenorrhœa, miscarriages, sterility, etc., and in males of various sexual dysfunctions; (2) *adrenal* from hypertrichosis and pigmentations; (3) *pituitary* from striation of the skin, thirst, etc.; and (4) *thyroid* from marked variation in oxygen consumption, change in pulse rate, etc. All these results are marked in the last column of the tables.

DISCUSSION

Hypersensitivity to insulin was noted in 24 per cent. of the present series of obese subjects, and these were scattered more or less equally throughout all three groups. It occurred, moreover, in association with excessive carbohydrate consumption. This change in insulin sensitivity is understandable in view of the relation between increased carbohydrate tolerance and hypersensitivity to insulin after a carbohydrate-rich diet (Himsworth, 1933-34a, 1933-34b, 1935-36a, 1935-36b, 1939; Ogilvie, 1933, 1935). The other fact connected with excessive carbohydrate consumption in obesity (Ogilvie, 1933, 1935) is gradual deterioration of carbohydrate tolerance from originally elevated to subnormal values; it also refers to the sensitivity to insulin.

Hyposensitivity to insulin as observed in five cases also occurred, more or less equally, in all three groups irrespective of duration of the obesity. All of them, on the other hand, showed conspicuous symptoms of disturbed, glandular function, and these abnormal mechanisms might readily explain the observed hyposensitivity to insulin. This hyposensitivity in obesity consequently might, at least, be due to one of two factors: (1) hormonal disturbance inhibiting insulin action, or (2) exhaustion of the primary hypersensitivity to insulin.

As already stated, fat accumulation has no obvious relation to any change in sensitivity to insulin. But a high carbohydrate diet may, on the one hand, produce a hypersensitivity which ultimately progresses to hyposensitivity or, on the other hand, produces primarily a disturbance in the lower phases of glucose catabolism. Insulin presumably acts in the initial stages of glucose breakdown (Mathews, 1939), and the conversion of carbohydrate into fat most probably begins in relation to pyruvic acid and acetaldehyde which occur at a relatively low level of glucose oxidation (Smedley-Maclean, 1943a). Obesity associated with overfeeding may, therefore, involve two independent disturbances leading respectively to changes in insulin-anti-insulin balance and to interference with complete glucose combustion. The first disturbance having been dealt with in another paper (Newburgh, 1942), the present discussion is limited to the second abnormality only.

The etiological factor leading to an upset in complete glucose catabolism may be either (1) overfeeding, (2) alteration in hormonal and cerebral functions, or (3) damage to the enzymatic system participating in glucose breakdown.

(1) Overfeeding with carbohydrate, protein and fat entails an amount of material which cannot be thoroughly oxidised and which exceeds the energy requirements of the individual. One part of the material is consequently oxidised in the usual way to CO_2 and water, and the other part must be converted into some substance requiring no oxidation so as not to overflow the tissues with the intermediate products of glucose metabolism. Such a substance might be fat. This suggestion is supported by the normal or even unusually high oxygen consumption of some obese subjects (Rony, 1940 ; Newburgh, 1942). In these circumstances oxidation progresses normally or even excessively and the remaining surplus only is converted into fat.

(2) In the case of hormonal or cerebral lesions the amount of material brought to the level of oxidation might not be over-abundant, but inefficient hormonal or nervous impulses cause inadequate stimulus for enzymatic oxidation and the production, therefore, of a substance needing no oxidation, that is, fat.

(3) In the case of damage to enzymatic oxidation (Godlowski) material brought to the stage of oxidation need not be excessive, but the toxic agents act directly on the enzymes themselves and inhibit aerobic breakdown. Naturally the last two possibilities might be complicated by overfeeding and vice versa.

Hypoglycæmic symptoms did not always correspond with low glycæmia. On the contrary, they sometimes occurred when the glycæmia reached hyperglycæmic values. They must, therefore, have been produced not by glycæmia itself but by the anti-insulin factors brought into the action by the injected insulin in the D.I.T.T. or produced by the patient in D.T.T.

SUMMARY

(1) Fifty-one unselected obese subjects showed three different varieties of sensitivity to insulin in D.I.T.T.—normal, hypersensitivity and hyposensitivity.

(2) There is no relation between alteration in sensitivity to insulin and the duration of obesity.

(3) Abnormal accumulation of fat sometimes coincides with alteration in sensitivity to insulin, but there is no causal connection between these two pathological processes.

(4) Excessive accumulation of fat is due to the disproportion between the quantity of material brought to the level of oxidation and the capacity of the oxidations system itself and this might be due to (1) overfeeding, (2) hormonal and cerebral lesions, (3) damage of enzymatic system or (4) all of these factors complicating each other.

(5) D.T.T. deteriorates with the duration of the obese condition.

(6) Symptoms of hypoglycæmia are due not only to the low blood sugar level, but mostly to the anti-insulin factors brought into action by insulin itself.

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PULMONARY MYCOSIS

By T. GOW BROWN, M.D., M.R.C.P.E., F.R.F.P.S.G., D.P.H.

MYCOTIC disease of the lungs has aroused considerable interest in the United States of America, and a recent paper by Goldstein and MacDonald (1944) gives a comprehensive review of the literature from Wernicke's (1892) original description of coccidioidomycosis in the Argentine up to the present.

The symptomatic similarity of pulmonary mycosis and pulmonary tuberculosis is stressed and points in the diagnosis are reviewed ; however, the parallelism between those conditions is so close that laboratory aids appear to be essential to arrive at a definite differentiation.

In endemic areas pulmonary mycosis has a high morbidity and a low mortality rate, yet infection is believed to take place, not from case to case, but by the inhalation of chalmydospores present in dust and sand.

During the past few years in this country an increase in the intensity of the anti-tuberculosis campaign has brought the number of persons under survey as probable patients beyond the bounds of reason, and the possibility of a pulmonary infection other than tuberculosis is apt to be overlooked.

Observations I have made throughout the past few years seem to indicate that mycotic disease of the lung may be more common than is thought, and that, until a critical evaluation of this apparently less serious clinical condition is made, erroneous diagnoses must upset the entire national economy.

Of the similarity of the clinical manifestations of mycotic infection and tuberculous disease there can be no doubt, as specimens have been submitted for examination for B. tuberculosis by every manner of physician from phthisiologist to general practitioner and have proved to be of a mycotic nature on investigation.

Many patients have been admitted to sanatoria or have attended tuberculosis dispensaries on clinical or radiological grounds and, while a few have had co-existent tuberculosis, the majority have not had the tuberculous nature of their disease established by any of the recognised laboratory methods.

Fortunately, many of the difficulties that assail the clinician in differential diagnosis do not present themselves to the laboratory worker and a little experience makes it a comparatively simple matter to select the mycotic sputum.

For some time I had observed sputa that looked like watered milk so I proceeded to investigate those specimens to discover the

nature of the infection and to establish data which would make its recognition as easy as possible. As the sputum from the same patient varies little in character over periods of months, it was necessary to define the nature of its essential features.

An occasional specimen may be of a mixed character, due to co-existent micro-organismal infection, but generally the sputum is fluid and of a greyish-white colour. On standing, a dead-white flocculent deposit separates rapidly from a slightly opalescent supernatant fluid. The important constituent is the white flocculent particle.

Microscopic examination reveals this deposit to be composed of epithelial cells and macrophages with either very few or an entire absence of polymorphonuclear and lymphocytic cells. There is often a mixed bacterial flora of no significance. Spores of varying sizes, usually oval and with a doubly refractive appearance, may be demonstrated, but this is not a constant finding.

This typical appearance of the sputum is unlike any reactive result of the usual bacterial infections, and the underlying process would appear to be proliferative rather than inflammatory. Although no post-mortem material has been available, the reaction seems to approximate more closely to that occurring in epidermophytosis, and it is quite understandable that a corresponding denuding of the epithelial surface may take place giving rise to cavitation.

Culture on Sabouraud's medium invariably gives a growth that is typical. Colonies appear in two to three days and, when fully grown, are 4-6 mm. in diameter. The colony is moist, smooth and paste-like, of a dead-white colour, although older colonies become dry, wrinkled and brownish.

The classification of pathogenic fungi is most unsatisfactory, but this infection would appear to be due to Candida albicans.

Between March 1944 and March 1945 specimens of sputum of characteristic appearance were examined from 467 persons. From all, Candida albicans was isolated, many on repeated examination over periods extending up to nine months, and on no occasion was there failure to isolate the mycete on subsequent examination.

All specimens were submitted to cultural and biological examination for tubercle bacilli if microscopic examination did not reveal the presence of this organism and, of the total, those from 59 persons proved to be of tuberculous as well as mycotic origin.

Every patient had a clinical history compatible with pulmonary tuberculosis and a selection may give some indication of the extent to which mycotic disease may simulate the more serious infection.

(1) Mrs G. was diagnosed in 1939 as advanced pulmonary tuberculosis with cavitation. An eminent phthisiologist pronounced the outlook as hopeless and advised sanatorium treatment and artificial pneumothorax. The latter advice was not accepted and six years later the patient's general condition was not depressed in any way. As she had a persistently negative sputum she was allowed home and has been quite fit to carry on normal household

duties throughout the war years. Her sputum had the characteristic appearance of mycosis and Candida albicans was isolated repeatedly.

(2). R. B. (18) was turned down by a Medical Board and referred to his home Local Authority as pulmonary tuberculosis. His sputum was persistently negative for B. tuberculosis but was copious and of the typical mycosis type; Candida albicans was isolated on repeated examination over a period of eight months.

(3). C. C. (42) had had a hæmoptysis and was attending a tuberculosis dispensary. Her sputum was persistently negative for B tuberculosis but had the characteristic appearance of mycosis; Candida albicans was isolated on repeated examination over several months.

(4). A. A. (21), a member of W.R.N.S., had a pulmonary complaint diagnosed as basal pneumonia. This did not respond to treatment but left persistent dullness and cough. The sputum was typical of a pure mycotic infection; Candida albicans was isolated.

(5). J. McC. (5), a small boy, had a persistent cough with sputum and a complaint of chestiness. The sputum had the characteristic mycotic appearance and Candida albicans was isolated.

(6). W. S. had a history of febrile attacks for nine months with recurring " colds " and cough. His sputum had the characteristic appearance of mycosis; Candida albicans was isolated.

(7). Mrs M. G. was diagnosed as suffering from pneumonia which did not respond satisfactorily to penicillin. Her sputum was characteristic of mycosis and Candida albicans was isolated.

(8). J. L. was admitted to hospital suffering from pneumonia and, while the clinician was satisfied that the classical signs were present and that radiological examination showed extensive consolidation, the patient's general condition was not consistent as he felt and looked " perfectly well." The sputum was typically mycotic and Candida albicans was isolated repeatedly.

A further interesting analogy with pulmonary tuberculosis is that several members of a family have suffered from this infection.

A mother, son and daughter were under observation at the same time for tuberculosis; all had negative sputa for B. tuberculosis, but all were typical mycosis. Candida albicans was isolated repeatedly from each patient.

Two sisters were in a sanatorium without confirmatory bacteriological evidence of tuberculosis, while their brother at home was under observation. All three had typical mycotic sputa from which Candida albicans was isolated repeatedly and all attempts to prove a tuberculous basis for their illnesses proved sterile.

From these few examples it is evident that clinical diagnostic difficulties make the differentiation of mycosis and tuberculosis a matter of extreme finesse unless a clear recognition of the probable prevalence of the former condition is admitted and careful scrutiny of the sputum in all pulmonary complaints is carried out.

The infection may not be confined to the lung for I have isolated Candida albicans from several refractory vaginal discharges that

presented a similar cellular appearance to the characteristic sputum and from a specimen of cerebro-spinal fluid. In the last instance I imagined the appearance of Candida albicans, which was subsequently isolated on culture, to be a contamination, but, in the light of further consideration, am convinced that this was a true infection.

It will be seen that mycotic disease should be considered in the differential diagnosis of any pulmonary complaint and particularly in patients suspected of having pulmonary tuberculosis with a persistently negative sputum.

The character of the sputum should be noted carefully as the naked-eye appearance of the white flecks that are always present in mycosis is typical and can be recognised easily even in a mixed infection.

The demonstration of spores in smears is too inconstant to be reliable but the isolation of Candida albicans on Sabouraud's medium is simple and certain.

Further investigation is necessary and, in view of the comparatively mild nature of the general effects of mycotic disease, most important if the patient is not to be labelled pulmonary tuberculosis through the non-recognition of the probable nature of his infection.

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NEW BOOKS

Prevention, First Aid and Emergencies. By LYLA M. OLSON, R.N. Pp. xii+591, with 190 illustrations. London: L. B. Saunders Company Ltd. 1946. Price 15s. net.

The publication of this book is the result of a course of lectures and demonstrations given to student nurses on all phases of emergency nursing. The subject is presented in a clear and concise form and there are many useful illustrations. The book will be of value to nurses and also to boys and girls in Scout and Guide organisations, as well as to policemen and industrial workers. It contains simple facts and information with which everyone should be familiar in order to give quick and efficient service whenever it is required.

Analecta Psychiatrica. By J. R. WHITWELL, M.B. Pp. xvi+160. London: H. K. Lewis & Co. Ltd. 1946. Price 16s. net.

Dr Whitwell, Librarian of the Royal Medico-Psychological Association, has for many years been interested in collecting references to psychological subjects in the literature from Hippocrates and Plato to the present day. Some of the more interesting passages he has brought together in the present volume. The choice of material is excellent and covers many aspects of the subject. This unusual book should be of interest not only to the psychiatrist but to any medical man who wishes for a time to get away from the humdrum of daily routine.

Occupational Therapy for the Limbless. By PHYLLIS LYTTLETON, C.S.P., M.A.O.T. Pp. viii+40, with 12 illustrations. London: H. K. Lewis & Co. Ltd. 1946. Price 3s. net.

The abnormal outlook of a limbless person is apt to cause the development of some mental kink if nothing is done to correct it. The author in her wide experience has found that occupational therapy can redeem the situation and give the limbless victim a new opportunity in the life which he must build anew. She deals very wisely with the psychological approach to such patients and describes in detail the kinds of work that may be undertaken in different cases. Though limited in its appeal, this booklet should serve a very useful purpose.

Ancient Anodynes. Primitive anæsthesia and allied conditions. By E. S. ELLIS, M.R.C.S., F.R.A.I. Pp. 187. London: William Heinemann. 1946. Price 21s. net.

This book must represent an enormous amount of study of ancient and relatively modern literature. The author modestly suggests that it will not have much to interest the medical profession since it does not confine itself to surgical anæsthesia, but deals with the subject in a far wider sense.

The story starts from the earliest times when conditions were much as they still are amongst the primitive peoples and it is traced right down to the introduction of ether and chloroform. One of the most amazing things about anæsthesia is the enormous length of time during which man had it practically within his grasp and yet failed to seize it; and even when a few far-seeing medical men had appreciated it, it was laughed at and treated with disbelief by their professional brethren.

An anæsthetic is, after all, only a sort of tamed inebriant, and a soporific is not far removed from either, hence it is necessary to consider all three in tracing the development of anæsthetics.

The book is well documented and excellently written. Dr Ellis is to be congratulated on his valuable contribution to the history of medicine.

The Anatomy of the Bronchial Tree. By R. C. BROCK, M.S., F.R.C.S. Pp. vi+96, with 142 figures. London : Oxford University Press. 1946. Price 42s. net.

This monograph has been written by a surgeon specially interested in chest surgery. It is based on a series of articles which have appeared in the *Guy's Hospital Reports*. The author has studied a vast amount of material in many ways and is in a position to give authoritative information. His book is very fully illustrated by diagrams, photographs and radiograms, and the number of illustrations is really much greater than would appear for many of the so-called figures consist of two or more separate pictures.

The importance of a sound knowledge of the correct anatomy of the bronchial tree is much greater than is generally believed and the author has done a valuable piece of work in correcting misleading statements which have appeared in standard text-books. This outstanding work will be universally recognised as an important contribution to medical knowledge.

Food and Nutrition. By E. W. H. CRUICKSHANK, M.D., D.SC., PH.D., M.R.C.P. Pp. vii+326, with 41 figures. Edinburgh : E. & S. Livingstone. 1946. Price 16s. net.

The war has emphasised with harshness and urgency what political reform has envisaged for many years, the need of a greater production and better distribution of food in the interests of the nutritional status of the people, and hope of peace demands that this principle be not lost sight of in the international sphere.

Professor Cruickshank devotes his first four chapters to the history of the subject ; then he reviews the physiological requirements of the body for the principal foodstuffs. Later chapters deal with special problems.

This brief survey of present knowledge of nutritional physiology has been written for the medical profession and for those of the general public who are interested in the subject and to these it should appeal.

Sanitary Science Notes. By H. HILL and E. DODSWORTH. Pp. 135. London : H. K. Lewis & Co. Ltd. 1946. Price 6s. net.

This small book covers the wide field of sanitary science in the briefest possible manner. It is an aid-to-memory for the sanitary student and others, and has most of the virtues and defects of the companion volume, *Food Inspection Notes*. It has the merit that it can be carried in the pocket and gives useful formulæ and definitions ; in other sections over-simplification may cause misunderstanding, so that in laboratory or office it would be better to refer directly to a larger text-book. The weakest section is that on infectious diseases in which there are a number of errors. The book will save the student the trouble of making notes and synopses himself. Whether that is a good thing is another matter.

The Sulphonamides in Theory and Practice. By J. STEWART LAWRENCE, M.D. (EDIN.), M.R.C.P. Pp. vii+125, with 11 tables. London : H. K. Lewis & Co. Ltd. 1946. Price 9s.

This book gives a concise review of the present state of our knowledge of the sulphonamides. First, the mode of action and the relative potency of the various drugs are considered. Then the pharmacology of the sulphonamides is described, as a knowledge of their absorption, excretion and distribution in the body fluids is essential for their most effective use in different diseases. Chapters are devoted to the organisms susceptible to the sulphonamides, to their use in traumatic surgery and to regional affections. The possible toxic effects and the common abuses of sulphonamide therapy are fully described. Finally there is a full list of references. This small book can be thoroughly recommended as a practical guide for obtaining the best results from sulphonamide therapy in any branch of medicine or surgery.

Obstetrical and Gynæcological Survey. Volume I, Number 1, 1946. Edited by N. J. EASTMAN and E. NOVAK. Pp. 158. Baltimore: Williams & Wilkins. Agents, Messrs Baillière, Tindall & Cox. Annual subscription £2, 12s. 6d.

This new journal is to appear six times a year. It is proposed to offer the practitioner abstracts of all world literature in obstetrics and gynæcology sufficiently full to give the average reader all the required information without the necessity of going back to the original papers. In addition it is proposed to publish comprehensive reviews of subjects of current interest by authors who are specially qualified to write on them.

The present issue contains one such review on Diabetes Mellitus and Pregnancy. The abstracts have been grouped under sectional headings which bring together kindred subjects. An interesting feature is that many of the abstracts are followed by editorial comment designed to evaluate the abstracted papers in the light of accepted opinion and practice.

The new journal is well produced and should serve a very useful purpose.

Some Minor Ailments of Childhood. By BERYL TWYMAN, M.B. Pp. 32. Edinburgh: E. & S. Livingstone Ltd. 1946. Price 9d.

The author has noted amongst mothers a widespread restlessness, discontent with home life and lack of happiness, and she makes the plea that women should endeavour to provide more and better home life for children. The book gives hints to mothers in coping with the minor troubles of childhood. It deals with care of the sick child, frequent colds, poor appetite, bed wetting, naughtiness and similar problems, and should be of the greatest help to the harassed housewife.

Medical Aspects of Growing Old. By A. T. TODD, M.B., M.R.C.P. Pp. 164, with 13 figures. Bristol: John Wright & Sons Ltd. 1946. Price 15s.

Recent statistics show that the proportion of older people in the population is steadily increasing and is likely to continue to do so. The elderly patient certainly presents many special problems with which the practitioner should be familiar. These the author discusses in simple and, as far as possible non-technical language, so that the information may be directly available to the layman. The book is full of useful information and should also be of the greatest help to the practitioner of medicine.

Homo Sapiens and the Peace Problem. By G. H. MONRAD-KROHN, M.D., F.R.C.P. Pp. vi+16. London: H. K. Lewis & Co. 1946. Price 2s. 6d.

The author discusses herd instinct and mass psychology and shows how readily a crowd of people may lose their individuality and be swayed by noisy leaders. He suggests that it is necessary for mankind at large to become aware of the dangers of mass mentality and to learn that we all carry inborn tendencies or instincts which under given circumstances may urge us into unintelligent and unworthy reactions. He recommends the rewriting of history—describing wars for what they are—collective murder. The author's purpose is not the ambitious one of pointing to an open road to eternal peace, but rather to attempt to attract attention to the problem.

L'anémie Infectieuse. By G. HEMMELER. Pp. 76, with no illustrations. Bâle: Schwabe & Co. 1946.

In this short account of anæmia in infections, the author first gives, in tabular form, the hæmoglobins, red cell counts, and sedimentation rates at various stages of certain infections. Twenty-five cases are then considered in more detail, differential marrow counts being included. The changes in the level of the serum iron, and their relationship to the anæmia are then considered.

The account would have been more complete had hæmatocrit readings been recorded, and the terminology differs from that in common use here, but this record helps to fill a need for an account of the pathogenesis of anæmia in infection.

NEW EDITIONS

A Practical Handbook of Midwifery and Gynæcology. By W. F. T. HAULTAIN and CLIFFORD KENNEDY. Third Edition. Pp. x+388, with 47 illustrations. Edinburgh : E. & S. Livingstone. 1946. Price 20s.

This edition retains the essential characteristics of its predecessors. For its size, by means of enumeration and tabulation, it summarises an amazing amount of up-to-date theoretical and practical information. Alteration has been made in the arrangement of some obstetrical chapters to bring together normal and then abnormal parturition. New chapters have been added, one on the infant written by a pædiatrician, one on the therapeutic use of hormones in obstetrics and gynæcology and one on sexual disorders.

Two criticisms are offered. The chapter on puerperal sepsis lacks a comprehensive definition to unify the ætiology and variety of lesions resulting from post-partum and post-abortion organismal invasion of the genital tract. Again the useful summary, of contraceptive techniques should be given as a separate chapter. These observations in no way alter the opinion that this edition will be found a most helpful synopsis for students. Practitioners, especially those resuming civilian practice, will also find here a short and very practical modern summary of the subjects.

A Complete Outline of Fractures, including Fractures of the Skull. By J. GRANT BONNIN. Second Edition. Pp. xiv+658, with 711 illustrations. London: William Heinemann (Medical Books Ltd.) 1946. Price 30s. net.

The second edition of Mr Bonnin's *Outline of Fractures* is a notable advance on its forerunner.

Written primarily for students, it succeeds admirably in providing an up-to-date, well-balanced and reasonably concise account of fractures which will have a much wider appeal than its author anticipated.

The book has a distinct academic flavour, yet it remains essentially practical; and the methods of treatment advocated conform to accepted British practice. The illustrations are numerous and illuminating, apart from those in the Appendix on Operative Exposure of the Long Bones, which are well below the general standard and should be replaced or deleted.

The book is well produced and a credit to author and publisher alike. It should, for many a day, be the junior classic in this important and difficult subject.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.). Ninth Edition. Pp. 262, with 38 illustrations. London : Oxford University Press. 1946. Price 12s. 6d.

This new edition contains a few minor alterations and additions chiefly in the chapters on acute intestinal obstruction and on acute abdominal emergencies in pregnancy and the puerperium. Two new radiograms have been included.

This very readable little book should continue to be of real help to all those who have to diagnose abdominal emergencies.

Regional Analgesia. By H. W. L. MOLESWORTH. Second Edition. Pp. viii+92, with 42 illustrations. London: H. K. Lewis & Co. Ltd. 1946. Price 8s. 6d. net.

This little book is a record of its author's personal experiences in the practice of local anæsthesia. It makes no claim to be comprehensive; it is, indeed, both

short and terse, yet it is a mine of information of the greatest interest and importance to surgeons who favour regional rather than general anæsthesia.

The format of the slender volume is pleasing; a few of the diagrams might have been drawn with more regard for anatomical exactitude, but for the most part they are useful and helpful.

We can confidently recommend the book as a sound, reliable and practical guide to local anæsthetic practice and procedure.

Practical Anæsthetics. By J. ROSS MACKENZIE, M.D., D.A. Second Edition. Pp. x+172, with 71 illustrations. London: Baillière, Tindall & Cox. 1946. Price 10s. 6d.

In this edition, Dr Mackenzie has added much new detail and yet contrived to restrict the size to pocket dimensions. A typographical error, which has passed into this edition (p. 10 *et seq.*) from the first, must be mentioned, viz. Bromethyl for Bromethol. Bromethyl is a synonym for ethyl bromide which is not what the author is describing. Chapter IX is entitled Endotracheal Anæsthesia, but half of it is concerned with Trichlorethylene, which would have found a more appropriate place in Chapters IV and V on Inhalation Agents. As a primer for students and occasional anæsthetists this excellent little book can be confidently recommended.

The Science of Dental Materials. By EUGENE W. SKINNER, PH.D. Third Edition, Revised. Pp. 410, fully illustrated. Philadelphia and London: W. B. Saunders Company. 1946. Price 24s. net.

It is not surprising that this book has reached its third edition. The revision of a text-book during a period of world war is a difficult undertaking, especially as fundamental researches are likely to be neglected and any available time is directed towards the invention of substitutes for scarce materials. Consequently some of the chapters in the present edition have not been revised from the second edition as no notable contributions have been made since 1940 to these particular subjects. Considerable progress has, however, been made in the knowledge and use of acrylic resins for dental restorations and the chapters dealing with this subject have been entirely rewritten. The book should prove to be of real value in the important branch of dental practice with which it is concerned.

An Introduction to Human Anatomy. By CLYDE MARSHALL. Third Edition, revised by EDGAR L. LAZIER, PH.D. Pp. xi+418, with 303 illustrations. London and Philadelphia: W. B. Saunders Co. Ltd. 1946. Price 12s. 6d. net.

This is an excellent short text-book of anatomy and Dr Lazier is to be congratulated on the alterations that he has made in this edition. Although too brief and simple to be adequate for medical students it should prove a reliable guide to practitioners who are required to conduct courses on elementary anatomy. Perhaps the two outstanding features of the work are the large number of useful illustrations, many of which are taken from standard anatomical text-books, and the footnotes that give the derivation and meaning of anatomical terms.

Electrocardiography in Practice. By A. GRAYBIEL, M.D., and PAUL D. WHITE, M.D. Second Edition. Pp. ix+458, with 323 illustrations. London: W. B. Saunders Co. Ltd. 1946. Price 35s. net.

During the last twenty years the scope of electrocardiographic diagnosis has greatly broadened as a corollary to advances in knowledge in this specialised branch of Medicine. Initially of value in recording and elucidating the mechanism of the arrhythmias, the electrocardiograph is now largely employed in the diagnosis of myocardial disease. In modern practice the use of chest leads has added greatly to precision, but at the cost of increasing complexity; the multiplicity of leads now

employed is a source of confusion to many. Of recent years new terms have crept into current use and new techniques are employed in the diagnosis of certain cases. There is great need therefore for an authoritative text-book on the subject, such as that now under review.

This book covers a wide field in a most satisfactory manner. There are initial chapters on physiology and technique and on variations in the normal, which lead on to sections on the arrhythmias and myocardial disease. The last is headed " Etiologic Types and Patterns " and covers not only the common forms of heart disease, but a wide variety of other conditions—avitaminoses, endocrine disorders, drug actions, etc. A valuable note on artefacts is included. Approximately one-third of the book is devoted to electrocardiograms " for practice in interpretation," arranged haphazard and accompanied by full diagnoses and comments in the text.

The standard of production is very high. The reproductions are admirably clear and reproduced in full size. The book is so arranged that a page of cardiograms faces the text describing the changes recorded, with a full clinical description of each case figured. It is emphasised by the authors that electrocardiography cannot be divorced from clinical study of the patient.

The book is strongly recommended to all interested in this branch of Medicine.

Theory and Practice of Nursing. By M. A. GULLAN, S.R.N. Fifth Edition. Pp. xii+236. London : H. K. Lewis & Co. Ltd. 1946. Price 12s. 6d. net.

This standard text-book first appeared as long ago as 1920, a record which speaks to its usefulness and popularity. The present edition has been thoroughly revised to bring it up-to-date but the original plan of presentation remains unchanged.

The book is one which can be read and re-read with profit many times during the nurse's training and it should serve as a useful book of reference when information is required.

Electro-therapy and Light Therapy. By R. KOVACS, M.D. Fifth Edition. Pp. 694, with 352 figures in the text. London : Henry Kimpton. 1946. Price 42s. net.

This work, originally limited to a description of electro-therapy and light therapy has now been expanded to include hydrotherapy, hypothermy, massage, exercise and the many kinds of treatment which go to make up physical medicine.

The first part of the book is devoted to a description of the various techniques and their uses, while the later sections discuss the method available for different individual disorders. Full details are given and the book is copiously illustrated. The steadily increasing interest in physical medicine should create a demand for this authoritative work.

Elementary Bacteriology. By JOSEPH E. GREAVES and ETHELYN O. GREAVES. Fifth Edition. Pp. xvii+613, with 169 illustrations. London : W. B. Saunders Co. Ltd. 1946. Price 20s. net.

The title does not quite convey the nature and scope of this work, which comes from the Utah State Agricultural College. It is in a sense elementary but its length and range make the term unsuitable.

It deals with bacteriology in the widest sense, less than half of its forty-nine chapters being concerned with that subject in relation to medicine. It traces bacteriological discovery from the earliest days up to the latest researches with the electron microscope.

The sections on bacteriology in relation to plant life and agriculture are naturally among the most detailed and interesting. Each chapter is followed by a series of questions for the student, and a list of references. The illustrations are excellent.

This fifth edition can be recommended as very readable, comprehensive and up-to-date.

CARCINOMA OF THE RECTUM

INCLUDING A SURVEY OF THE PRESENT TRENDS IN ITS OPERATIVE TREATMENT *

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IT is a provision of the Thom bequest that the bequest was made for the advancement of the prevention of chronic disease, with special reference to cancer.

With carcinoma in certain situations such as the lip, stomach, and breast the occurrence of a preceding chronic condition is not infrequent. In carcinoma of the rectum the relationship to a preceding chronic condition is neither so obvious nor so frequent.

Let us examine the more chronic conditions of the colon in relation to carcinoma.

(a) *Papilloma or Adenoma in the Adult Colon.*—These are definite pre-cancerous conditions. Gabriel quotes Dukes as having informed him that 10 per cent. of operation specimens after excision of the rectum for cancer showed definite evidence of having developed in a pre-existing villous papilloma.

The condition of multiple polyposis is an uncommon disease which tends to run in families. Carcinoma is extremely liable to develop here, especially in the rectum and sigmoid.

(b) *Chronic Ulcerative Colitis.*—In chronic ulcerative colitis the spread of the ulceration leads to the isolation of strips and islets of mucosa, and these latter form pseudo-polypi. Subsequent healing and scar tissue formation may make these pedunculated. This condition has been called colitis polyposa. Lynn of Detroit in a recent critical review stated that in 1467 cases of ulcerative colitis 28 developed carcinoma of the colon, an incidence of 1·9 per cent. In 1940 Jackman, Bargen and Helmholtz studied a group of 95 children in whom six carcinomas developed later in life. This was an incidence of 6·3 per cent. among those who suffered from colitis as children. In 1944 Cattell, of the Lahey clinic, wrote, " For a number of years our observation indicated that malignancy was a rare development on the basis of chronic ulcerative colitis. However, in the last two years we have observed 8 patients with a carcinoma arising in ulcerative colitis."

The parasympathetic nerve supply comes from S 2, 3 and 4 via the pelvic nerves or nervi erigentes. These nerves are motor to the muscle of the rectum above and inhibit the sphincter muscle which is normally in a state of tone. The parasympathetic is the nerve of emptying.

Jenkins, after conservative resection of the rectum in two cases, found that the external sphincter functions normally, but the internal sphincter is lax and does not, although it did so in a Hartmann's operation which he performed. He said that in resection of the rectum extending from the ano-rectal ring junction upwards the nerve supply of the internal sphincter must necessarily be sacrificed, although it is possible that local nerve plexuses may give some degree of postural tone.

PATHOLOGY

The contribution of pathology in the evolution of the modern treatment of carcinoma of the rectum has been great. It has been the " Pathfinder " force marking the target for further surgical attack, but it has done more than that. It can provide a more or less accurate prognosis of the outcome in any given case. It must be admitted that carcinoma of the rectum, with its slow growth and spread along certain now well-defined channels, forms an ideal field for such close collaboration between pathologist and surgeon.

Carcinoma of the rectum is an adenocarcinoma of the columnar cell type. In the early stages it is a local disease. It starts as a raised nodule or as a malignant degeneration of an adenoma or papilloma. A double carcinoma is liable to occur and may be missed if not looked for at the time of exploratory operation, and this is one of the points in favour of the combined operation as against the perineal two-stage one. Gabriel, in his series of 400 perineo-abdominal excisions, found a double or multiple carcinoma in 21 cases, an incidence of 5·3 per cent.

Carcinoma in the rectum is usually a slow-growing tumour. It extends by direct spread through the rectal wall, and as a rule lymphatic metastases do not occur until the tumour has reached the peri-recta' fat, but there are exceptions to this. Usually at first the glands involved are those in the meso-rectum close to the tumour, but Wood and Wilkie in the detailed examination of 100 specimens found that in 6 cases where the tumour was low down, glands at the upper end of the rectum were involved without involvement of those near the tumour.

Cuthbert Dukes examined very fully 1000 specimens from cases of excision of the rectum, and followed up the patients to find out what pathological features had special prognostic significance. He gave his results to the section of Proctology in the Royal Society of Medicine in November 1943. His method was to open up the specimen then stitch it to a metal frame so as to keep it on the stretch. The specimen was then fixed and later the vessels and glands could be dissected out.

Site of Tumour.—Tumours may occur in the upper third, in the

ampulla or in the lower third. Dukes followed 370 cases treated by the combined operation (A.P. or P.A.) during the years from 1930 to 1939. For cases without glandular metastases the results of surgical treatment were the same whatever the situation of the primary tumour. With glandular metastases the result of treating tumour of the ampulla was not as good as for growths of similar development in the upper and lower thirds.

The size and surface area of growth are not so important. A tumour growing out into the lumen of the bowel metastasises late, while a small shallow ulcer may have spread far in lymphatic and venous channels.

Shape.—The spread is more in a transverse axis than in an upward and downward one. Hence the usual oval shape of the ulcer. Intramural infiltration is rare, and this is important. Cases of cancer of the upper third *without* lymphatic metastasis, treated by perineal excision, have done well, even if it was possible to get only just above the growth.

Spread.—The spread of carcinoma is by the following routes : (*a*) venous, (*b*) lymphatic, (*c*) local or direct, (*d*) peritoneal.

Venous Spread was found in 17 per cent. of the 1000 operation specimens. It occurs with equal frequency from all regions. Dukes found its closest correlation with the histology of the primary tumour. The more rapid the growth the greater the likelihood of venous spread. In post-mortems of 20 patients who had died within a week or two of excision and whose specimens had shown malignant growth in the hæmorrhoidal vein, only 10 had metastases in the liver. It can be said that the finding of cancer cells in the hæmorrhoidal vein is of bad prognostic omen due to the chance of hepatic metastases.

Lymphatic Spread.—Dukes found an amazing variability in the number of lymphatic glands during the dissection of specimens. In some only one or two glands were present, in others fifty. The average in a consecutive series of 596 operative specimens was 17·4 per cent. Dukes considers the stimulus to the proliferation of lymphoid tissue to be septic absorption. He found the larger and more septic the ulcer the more lymphatic glands. Invasion of lymphatic glands by cancer cells does not act as a call for formation of new lymphatic glands. There is a close relationship between the histological grade of the tumour and the presence of lymphatic metastases, even greater than in cases of venous spread.

Dukes always counts the number of nodes involved, and from the follow-up records is able to say that patients with five or more glandular metastases rarely live for five years.

Local Spread.—The growth infiltrates the coats of the bowel, peri-rectal fat and sheath. Ampullary tumours are apt to spread along the middle hæmorrhoidal vessels and give abscesses in the perineum. Prostate, uterus, vagina and bladder may be involved by the growth.

Spread by peritoneal deposits occurs occasionally.

CUTHBERT DUKES' CLASSIFICATION

A. Cases where the tumour is limited to the rectum.

B. Cases where the tumour extends to the peri-rectal fat, but has no lymphatic metastases.

C. Cases with lymphatic metastases. These are then divided into C_1. Where the glands were situated locally, and had not reached far up the superior hæmorrhoidal arteries. C_2. Where glands nearest the point of ligature of the superior hæmorrhoidal vessels were involved.

Dukes in his analysis of 1000 specimens found the group percentages were A cases = 15 per cent.; B cases = 35 per cent.; C cases = 50 per cent.

Broders developed the method of grading malignant tumours histologically on the principle of cell differentiation. Four grades are used. Grade I where the malignant cells are mature and differentiated, Grade IV where they are undifferentiated and anaplastic, with Grades II and III between. Wood and Wilkie pointed out that a small piece of tissue for biopsy may be misleading, as the histological structure of the growth may be very different in other parts. A biopsy taken from the growing edges of the tumour is most reliable.

OPERATIVE TREATMENT OF CARCINOMA OF THE RECTUM

The early operation, e.g. Lisfranc (1826) removed only the anal canal ; Kocher (1875) stitched up the anus and opened the peritoneum of the pouch of Douglas, preserving the external sphincter, and stitched the bowel above the tumour to the rim of the anus ; Kraske (1885) obtained better access by removing the coccyx and part of the lower sacrum and giving a sacral anus. The term resection as distinct from amputation when applied to the rectum usually denotes division of the bowel above and below the growth and junction of the two ends by circular suture or invagination of the upper segment into the lower. This latter invagination is usually called the " pull through " or " dürchzug," and the commonest modification of it is that associated with the name of *Hochenegg*, who removed the modified skin lining the anal canal, as in Whitehead's operation, before invagination of the upper bowel. These operations were conceived before the pathology and mode of spread of the rectal carcinoma were fully understood. Local recurrences were common and sepsis was not infrequently serious, and attempts to preserve the external sphincter either by resection and anastomosis or by " pull through " methods were not very successful.

For the last twenty years in this country two methods alone have been practised to any extent : (1) the two-stage perineal excision as advocated by Lockhart-Mummery of St Mark's ; (2) the combined abdomino-perineal one-stage operation advocated by Ernest Miles

of the Cancer Hospital. (In 1920 Ernest Miles reported 72 cases of the abdomino-perineal operation with 33 per cent. operative mortality. This was reduced to 12·3 per cent. mortality in 55 operations in the five years before 1937. Lockhart-Mummery's operative mortality in 340 perineal excisions was 8 per cent.)

Many were the discussions, two-stage perineal versus abdomino-perineal, Miles contending that the perineal operation was not radical enough, Lockhart-Mummery holding that it was, and that the mortality of the abdomino-perineal was too great. I have heard the Chairman in a surgical meeting in London introduce the two speakers after the manner of the boxing ring, " On my right, Mr Lockhart-Mummery of St Mark's ; on my left, Mr Ernest Miles of the Fulham Road." Since about 1930 the staff of St Mark's (formerly the stronghold of the two-stage perineal) have been performing more combined excisions than the perineal. They do the one-stage combined perineo-abdominal, and more recently they have been doing on occasion the synchronised one-stage combined perineo-abdominal excision, where two surgeons work together, one in the abdomen and the other from the perineum. Special leg rests permit the patient to be in a position in which this can be done. The total operative mortality for ten years from 1930-1940 at St Mark's for the perineo-abdominal was 17·2 per cent., although in 1939-40 the mortality was only 7·5 per cent., which brings it down to that of the two-stage perineal excision. The pathological researches and follow-up of cases by Cuthbert Dukes have indicated clearly to what degree the perineal excision is less satisfactory than the combined operation. He states that after examining a large series of specimens he formed the opinion that 80 per cent. of A and B cases (*i.e.* without lymphatic metastases) and 20 per cent. of C cases would have done as well with the perineal as with the combined operation. This is important knowledge, but unfortunately Dukes' classification is a pathological one and not able to be determined before or during operation. It is, however, of great assistance from the point of view of prognosis. On pathological grounds the perineal excision is probably inadequate when compared with the combined, as 50 per cent. of rectal carcinoma are C cases, and the risk of a second carcinoma higher up is 5·25 per cent. The less experienced the operator, the stouter and older the patient may be factors that determine the perineal excision as being the safer procedure. I should mention that the Hartmann's operation is sometimes done for tumours in the lower pelvic colon, where for reason of obesity, age or general condition the combined operation is considered too severe.

With the idea of reducing the shock and so the mortality, attempts have been made to carry out a two-stage abdomino-perineal excision. (This would enable cases to have an abdomino-perineal operation who could not have stood the one-stage operation.) The difficulty in getting a satisfactory two-stage abdomino-perineal operation is that you cannot divide the operation into a clear-cut first-stage abdominal

with colostomy, and a second-stage perineal. To get that you would have to ligature and divide the superior hæmorrhoidal vessels and the pelvic meso-colon completely before the distal colon to be removed could be buried below the peritoneum of the pelvic floor. By the time the second stage perineal part came to be done, the colon, deprived of its blood supply, would be gangrenous and sepsis would have occurred. This was the disadvantage of the " *Coffey* " two-stage operation. A further disadvantage of the two-stage is the presence of an open colostomy at the time an extensive abdominal dissection is being done. Nowadays a course of sulfasuxidine would probably minimise this risk.

To get over the difficulty of blood supply D. F. Jones, while ligating the superior hæmorrhoidal vessels, does not divide the meso-colon completely and preserves the marginal arterial arch. He mobilises the pelvic colon and raises up the peritoneal pelvic floor and attaches it higher up the colon, pushing the distal colon and tumour below the pelvic floor peritoneum. He then does a loop colostomy. The second-stage operation is the perineal excision only. *Lahey* of Boston divides the meso-colon down to the superior hæmorrhoidal vessels, but preserves them. He divides the colon across, the proximal end being implanted in the paramedian wound as a permanent terminal colostomy, the distal end being fixed in a vertical suprapubic incision as a temporary measure. At the second stage the abdomen is opened again through a median incision, after stitching up the open end of the distal colon. He continues thereafter as an abdomino-perineal excision, finally removing the bowel and tumour from the perineum. *Rankin's* operation is rather similar to that of Lahey, except that at the first stage the distal end of the colon is invaginated, closed and dropped back into the abdominal cavity instead of being implanted in a separate suprapubic wound. There is only a minimal division of the meso-colon at this stage. The second stage is a perineo-abdominal excision, as distinct from the abdomino-perineal of Lahey's operation, but the abdomen here also is opened for a second time.

Devine did a defunctioning transverse colostomy as a first stage, but this still leaves an extensive second stage and also gives the patient an extra, although temporary, colostomy. In cases of acute obstruction Devine's defunctioning transverse colostomy would be an excellent preliminary treatment.

Norbury states that in the ten years from 1931-1941, 73 cases at St Mark's were treated by a two-stage perineo-abdominal operation. There were eighteen deaths—a mortality of nearly 25 per cent.—sepsis and peritonitis being the causes.

Colostomy.—This may be either a terminal colostomy as in the case of the combined operation, or a loop colostomy as in the second-stage perineal excision. The disadvantages of a loop colostomy are (1) that it is more bulky ; (2) that the spur has to be maintained ; (3) that there is a blind distal loop which may need to be washed out.

Both among the laity and some of the medical profession much prejudice exists against a colostomy, and operative treatment may be refused on that account. It may be that previous knowledge and experience of a palliative colostomy, where blood and mucus go on discharging from the lower end of the bowel, forms the mental picture conjured up by the word " colostomy." With correct care and attention a colostomy can be kept regular and got to work only once or twice a day. It should be washed out each morning with cold or tepid water through a rubber tube such as a No. 12 rubber catheter. If the motions are too loose, normacol, I-so-gel or visiblin may be useful. These granules (a teaspoonful taken at night) swell in the intestine and help to make the stools firmer and bulkier. People with good colostomies can go about their everyday work, e.g. a shop assistant who works from 9.30 a.m. to 5 p.m., a farmer who does his whole day's work, a gamekeeper who is out all day, etc. At a recent discussion in the Section of Proctology of the Royal Society of Medicine " On the Management of the Permanent Colostomy," most of the speakers favoured a daily washout, although Gabriel spoke against it, saying that at St Mark's they had had nine cases of tube perforation from the washing out of colostomies. Eight of these proved fatal. All who spoke in this discussion were against any cup or bag being incorporated in the belt worn, as it tended to cause suction and promote a hernia at the site of the colostomy. They said that only a celluloid or metal plate should be incorporated over the colostomy. Wangensteen said that the only patient who hunted him with a gun was a patient upon whom he had done a colostomy for acute obstruction due to an irremovable lesion of the left colon.

Devine's work on defunctioning the colon has brought home once more the importance and advantage of having an empty colon to operate on. Much time should be expended in getting the colon cleaned by repeated enemata and by liquid paraffin from above.

If an acute obstruction is present then a transverse colostomy should be done, either a loop colostomy or a divided loop which may be of the Devine type. The distal colon can then be washed out both ways and thoroughly cleared before the next stage.

Where a colostomy has been done as the first stage of a two-stage perineal excision and once the colostomy is acting, the distal colon should be washed through daily, alternately from the colostomy down and from the anus up. This washing out is continued till the distal colon is clear of fæcal matter. The importance of this step cannot be emphasised too much.

The diminishing operative mortality and increasing operability rate of the combined operation is due to a number of things :—

(1) The use of adequate blood and plasma transfusion, as it is now available so freely.

(2) The variety and flexibility of modern anæsthesia.

(3) The restriction of fluids post-operatively by mouth and instead

the intravenous administration of fluids. Increased knowledge of electrolyte balance, hypoprotinæmia, etc.

(4) The use of sulfasuxidine and thalistatin for four days before operation (Wangensteen does not use these). 0·5 gm. of sulphadiazine four-hourly post-operatively is given to prevent or combat urinary infection.

(5) Team work. (As an illustration of the importance of this, one of the London rectal surgeons reported that his mortality from perineo-abdominal excision of the rectum was 10·6 per cent. at St Mark's, where he did most of his cases, while in another hospital he worked at his mortality was 20 per cent.)

For the last quarter of a century the radical treatment of carcinoma of the rectum in this country has been either (a) a perineal two-stage excision, or (b) the combined one-stage operation, either the abdomino-perineal or the perineo-abdominal. Technique, methods and team work have greatly improved, but the types of operation have remained fundamentally unchanged.

It was the work of Ernest Miles, first reported in 1908, that developed and standardised the combined operation as a result of his pathological researches. He described the *downward* zone of spread (to peri-anal skin and ischio-rectal fat), the *lateral* zone of spread (to the levator ani muscles and the internal iliac glands), and an *upward* zone along the superior hæmorrhoidal vessels. The more recent and independent investigations by Westhues, by Dukes and by Coller and others, have shown that involvement in a downward and lateral direction in rectal carcinoma is very rare and occurs mainly by retrograde spread when the high lymphatics are blocked by tumour cells. It is doubtful then if removal of the anal canal and rectum below the tumour is really necessary on pathological grounds.

Disadvantages with an inguinal colostomy and the fact that the perineo-abdominal or abdomino-perineal operation leads to loss of sex function and impotence in males have led to renewed attempts to preserve a functioning anal sphincter. These attempts were first reported from the Continent, and recently a number of American papers, a paper from Canada, and one from New Zealand have dealt with this subject. In this country in 1935 a discussion on " Conservative Surgery in Carcinoma of the Rectum " was reported in the proceedings of the Royal Society of Medicine. Grey Turner reported 19 cases of " cuff " resection of the rectum through a posterior perineal approach with end-to-end anastomosis. In 14 of these 19 cases a fistula developed, and in 12 of them the fistula healed within three months. At the same meeting Rayner reported 4 cases done by the method of Sebrechts of Bruges, which is a " pull through " operation done after a fairly extensive abdominal stage. Devine of Melbourne in 1937 reported in the *British Journal of Surgery* resection of the rectum and suture after defunctioning the distal colon. A discussion on the operative treatment of recto-sigmoid carcinoma took place at

the Association of Surgeons meeting in London last May. The abdomino-perineal and perineo-abdominal were fully discussed, but there was no mention of any attempts to preserve the anal sphincter.

On the Continent Hochenegg of Vienna in 1929 reported almost 1000 radical operations, in about 250 of which the anal sphincter was saved. Kuettner of Breslau also in 1929 reported 660 radical operations in which he had restored continuity in about 250. Finsterer of Vienna in 1934 reported 179 excisions of the rectum in 127 of which the sphincter was saved, that is in 70 per cent.

In America in 1932 Wayne Babcock of Philadelphia reported his method of procto-sigmoidectomy for carcinoma of the recto-sigmoid, which is a " pull-through " type of operation, but without preliminary colostomy and after abdominal dissection. He gives a perineal anus without preserving the sphincters.

In 1937 Gehrels of San Francisco reported a sacral approach after a preliminary colostomy giving more mobilisation than a Kraske, in which he mobilises the rectum with the tumour, ligatures the superior hæmorrhoidal artery and leaves the loop of the rectum with the tumour in the sacral wound wrapped in gauze. In twenty-four to forty-eight hours he saw a line of demarcation and commencing gangrene and could resect the gangrenous loop with cautery and anastomose the ends knowing that the blood supply was all right—a modified Milulicz operation in the sacral region.

In 1944 Dixon of the Mayo Clinic reported 181 cases of radical anterior resection in cases of recto-sigmoid carcinoma. This was a resection of the growth with end-to-end anastomosis, all done as an abdominal operation. He raised the peritoneal floor above the level of the sutured colon and did a simultaneous transverse colostomy. There was an over-all mortality of 12·1 per cent. The operative mortality in 1935-6 was 19·4 per cent., but in 1941-2 it was 2·4 per cent. (he was doing 35 to 45 cases per year).

In 1945 Wangensteen of Minneapolis reported 24 cases of resection of an ampullary rectal carcinoma from the abdominal side with direct anastomosis and without colostomy. After the direct anastomosis he raised the peritoneal floor above the suture line and passed a rectal tube through the anastomosis. Wangensteen may make the anastomosis as close as 5 cms. to the anus, he always likes to excise 3 cms. of normal mucosa below the tumour.

In 1945 also Bacon of Philadelphia reported 205 radical resections with preservation of the sphincters in 167, i.e. 80·3 per cent. The operation he does is similar to Babcock's procto-sigmoidectomy, but preserves the external sphincters. He leaves in a presacral drain for forty-eight hours. Bacon reviewed a series of 1401 cases of carcinoma of the rectum and anus in which the distribution of the disease was accurately noted and deduced from this that 80·9 per cent. of cancers of the rectum could be removed without sacrifice of the sphincter muscles.

This year Gordon Murray of Toronto reports a series of 15 cases in which he did a " cuff " resection without colostomy for carcinomata low in the rectum. As in Kraske's operation the approach is through the sacrum, removing the coccyx, the fifth and a bit of the fourth sacral vertebræ. He states that the cases suitable for this operation are those in which the growth is above and not involving the sphincter or anal canal mucosa. The growth should be easily palpable through the rectum and for a trans-sacral resection, the upper margin of the growth must be palpable with the finger in the rectum and be freely moveable on the surrounding structures.

With the knowledge that the spread of carcinoma is in an upward direction in the majority of cases, and given an empty or defunctioned colon, the successful accomplishment of either a two-stage combined operation or an operation conserving the anal sphincter depends entirely on the adequacy of the blood supply of the proximal loop of colon by way of the superior hæmorrhoidal and sigmoid arteries, and in the resection cases also it depends on the blood supply of the distal part of the rectum and anal canal. Dixon found that the middle and inferior hæmorrhoidal arteries were enough to supply the distal segment of the rectum.

RESULTS OF PRESERVATION OF EXTERNAL SPHINCTER

Wangensteen found the majority of his patients had nearly normal sphincteric action after undergoing ampullary rectal resection. In patients in whom a rectal fistula developed from a leak at the suture line, the leak was slow in closing and healed with persistent defect in the rectal wall, and rectal continence was impaired. He had a recto-vaginal fistula in two cases, which marred an otherwise satisfactory continence.

Bacon says, " It must be realized, and we are frank to admit it, that the sphincteric function following procto-sigmoidectomy is not perfect, nor that for which we strive, yet in approximately 80 per cent. of our cases continence is cited, and between 90 per cent. and 95 per cent. of our patients are able to carry out their daily occupation without inconvenience. About 40 per cent. wear a protective pad or strip of gauze, not of necessity, but often because a sense of security from soiling is afforded."

In Dixon's anterior resection of recto-sigmoid tumours the sphincter mechanism is not interfered with.

Jenkins of Dunedin says that after conservative resection of the rectum the patient has to depend on the voluntary external sphincter for control, and that this control is very inadequate when compared with the normal mechanism. He has never seen any reference by surgeons to the state of the internal sphincter after operation. The loss of normal reflexes concerned in defæcation is an equally serious matter 'in that purgatives and enemata become necessary. He con-

siders the Hochenegg "pull through" operation gives the most satisfactory results.

Conservative operations might be classified as follows :—

Anterior Resection	Dixon+complemental colostomy for rectosigmoid carcinoma. Wangensteen without colostomy for ampullary carcinoma.
Posterior Resection	Gehren's sacral approach after preliminary colostomy. Gordon Murray's sacral approach without a colostomy. Grey Turner—cuff resection, usually without colostomy.
Pull Through	Wayne Babcock and Bacon. Sebrechts with preliminary transverse colostomy. } With or without a Whitehead's operation.

(1) Are we in this country being too hidebound and stereotyped in our operative treatment ?

(2) Do our patients with colostomies really resume their former place in life, or does the colostomy form the pivot around which their daily life revolves ?

The answer to question (1) would appear to be that the operative treatment is more or less standardised in this country to the perineal two-stage and the one-stage combined. In this country surgeons mostly work in small units, so that the number of eases of eareinoma of the rectum dealt with by any one surgeon is relatively small, except in such specialised hospitals as St Mark's and the Caneer Hospital. The try out of any conservative method before it is standardised might be a lengthy and rather unsatisfactory procedure in such small units. In America and on the Continent the clinics are larger, and all cases of carcinoma of the rectum are often referred to one or two members of the staff who make a special study of it, and can try out new methods. Ernest Miles in the preface to his book on *Surgery of the Rectum*, published in 1939, says : " Unfortunately there is a tendency to-day to revert to less radical measures in the surgical treatment of cancer of the rectum, chiefly with a view to abolishing the necessity of colostomy. I condemn this attitude because, after a long experience, I am convinced there is no place for conservatism in the surgery of malignant disease." The answer to question (1) is probably in the affirmative.

The answer to question (2) depends very much on the type of patient. Those who are introspective will continue to regard themselves as invalids, while the extrovert will carry on as usual with but little thought of his colostomy. The physical side, especially the frequency of bowel movements and the escape of flatus, can largely be controlled by daily enemata, attention to diet, etc. The complete answer to this question, however, could only be given by interrogation of the patient's relatives and friends.

MY OWN SERIES

I have done no conservative operation so far.

I submit my small series of cases to you, but doubt whether this has any value, other than indicating the experience of a general surgeon. The disadvantage of a small series of cases is that the fate of one case may alter percentages considerably, but the percentage method has certainly slight advantages for comparison purposes. In eighteen years I have seen 105 cases of carcinoma of the rectum, excluding 3 cases of multiple polyposis and 5 of epithelioma of the anus.

Frequency.—The average number of cases seen per year was about 4 or 5, but in the last three years I have seen 36 cases. St Mark's about 1926 used to get 40-50 new cases a year. From 1934-43 the new cases averaged 125 annually. The Registrar-General's report on deaths certified due to rectal carcinoma has risen from 51,939 to 71,098 in 1938, *i.e.* an increase of over 19,000 cases a year, so that one can assume that rectal carcinoma is increasing.

Sex.—Sixty-one males were present in this series to 44 females. In Dukes' 1000 cases the relationship was almost two males to every one female. The operation in the male is more difficult than in the female, there is a smaller pelvis, and the incidence of urinary infection is higher in view of the long urethra and not infrequent enlargement of the prostate.

Age.—The average age of the 44 excision cases was 62·5 years. The average age in St Mark's series of excision was 57 years. In my series the youngest excision was 29 years and the oldest 76 years.

Operability Rate.—Forty-four cases were radically excised out of the 105 cases, giving an operability rate of 42 per cent., *i.e.*, over the course of eighteen years. In St Mark's the operability rate has gradually risen from about 60 per cent. before the war to 79 per cent. in 1942-43. A Birmingham series of 175 recto-sigmoid carcinomas in the five-year period 1936-41 was reported at an Association of Surgeons meeting, in which the operability rate had been lowered during the war to 25 per cent.

Types of Operation.—In this series there were 33 cases of two-stage perineal excision and 11 cases of combined excision.

Survivors.—Twenty-one of the 44 cases are alive now. Two cases have been lost sight of. Six of the 21 have been alive for eleven to fourteen years after operation. Two other cases, not included in the 21 survivors, could be called cures—a female who died nine years after operation from myocarditis at the age of eighty-one, and a male who died fourteen years after operation from cerebral hæmorrhage at the age of sixty-six.

Operative Deaths.—All those who died during their stay in hospital from whatsoever cause are included under operative deaths. Four of the 33 cases of perineal excision died, giving a mortality of 11·7 per cent., and 4 of the 11 combined excisions died (36 per cent.).

Of the 11 cases still not accounted for 6 died in the first year, 4 died in the second year, and 1 in the fifth year after operation. It can be said that if a case survives without any obvious metastases for five years, the rectal cancer is probably cured.

Causes of Death.—One case died on the table from shock, where the uterus was involved and was being removed along with the rectum.

One case died on the third day with an unexplained temperature of 105°.

One case died on the fourth day with a persistent tachycardia. Post-mortem showed a large antemortem clot extending from the right auricle through the right ventricle into the pulmonary artery.

Two cases died on the eleventh and twelfth post-operative days, one from gross sepsis in the perineal wound and the other from a biliary peritonitis from rupture of the gall bladder.

The other 3 cases were all men over seventy years who died between the sixteenth and twenty-first post-operative days ; one of them from gross urinary infection, who had also a tumour of his left kidney ; another from an acute glomerular nephritis ; and the last of a hypostatic pneumonia.

Inoperability.—Nine cases were rejected without operation on account of their general or local condition, age, etc. Forty-three cases were rejected after exploration, because of hepatic secondaries, peritoneal involvement with ascites, or fixation to sacrum, prostate, etc. It is in the fixed group that an increasing experience enables a few cases to be removed that formerly would have not been attempted. Of the 105 cases there were only 6 who came in with an acute obstruction.

Pathology.—The earlier cases were not classified pathologically according to the Dukes' scheme, but in the last 33 cases 1 was an A case, 15 were B cases and 17 were C cases. On three occasions a second carcinoma was found. It is probable that some of the B cases were really C cases, as the distinction between the two is determined by finding involved glands in dissection of the specimen, and I doubt whether in the earlier years this was critically enough done.

I have endeavoured to give you a survey of most of the recent work on carcinoma of the rectum mainly taken from American and British sources. The rectum is one of the more favourable sites for carcinoma, and I feel the time is now coming when we will have to consider saving the external sphincter and giving a perineal anus in a certain number of cases upon whom we now do excisions.

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THE TREATMENT OF TOXIC THYROID DISEASE WITH THIOURACIL *

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ALMOST exactly three years ago, Dr E. B. Astwood of Boston described the effects of thiourea, a chemical known for seventy-five years and of thiouracil, synthesized in 1908, administered orally to patients with hyperthyroidism, previous experimental investigations having suggested that such substances might be capable of modifying the functional activity of the thyroid gland.. So impressive were the therapeutic results in these first three clinical cases studied by Astwood (1943) that they marked the beginning of what promises to be a new era in the treatment of thyroid disease. An astonishing number of publications have appeared subsequently involving observations on more than 5000 cases of hyperthyroidism treated with thiouracil and related " anti-thyroid compounds."

With due allowance for possible early over-enthusiasm respecting this new medical treatment, the published reports leave little doubt that, in most instances, the administration of thiouracil can bring about a remission of the hyperthyroid state, if given in adequate dosage for a sufficient length of time. Furthermore, thiouracil appears to be effective against all types of hyperthyroidism whether these be associated with diffuse or nodular goitres. Almost all clinical investigators have commented upon the possibility of the development of certain complications in the nature of toxic reactions due to the drug.

However, since the advantages of thiouracil seem to outweigh its disadvantages, it is opportune that we attempt to appraise the usefulness of this new therapeutic agent in the light of existing knowledge, even although it is not possible at this time to define precisely the limits of its applicability.

THERAPEUTIC APPLICATION

My experience with thiouracil concerns various observations made upon 60 patients with hyperthyroidism, some of whom have been followed for longer than two years (Watson and Wilcox 1944 ; Watson 1945). Although this is a relatively small series of cases upon which to base any definite conclusions, the clinical therapeutic effects agree with those obtained in much larger series by others, with the exception that toxic reactions due to the drug have been fewer than anticipated,

considering the rather. high incidence of these as reported in the literature.

Fig. 1 A is a partial record of the case of a young woman with the symptoms and signs of primary hyperthyroidism which had been progressing over a period of one year. In addition to the nervousness, tremor, tachycardia, irritability, heat intolerance and a weight loss of 20 lbs., the basal metabolic rate was +44 per cent. There was a diffuse palpable enlargement of the thyroid gland and slight but noticeable exophthalmos. Previous medications of various kinds had been ineffectual. Iodine had not been taken. The response to
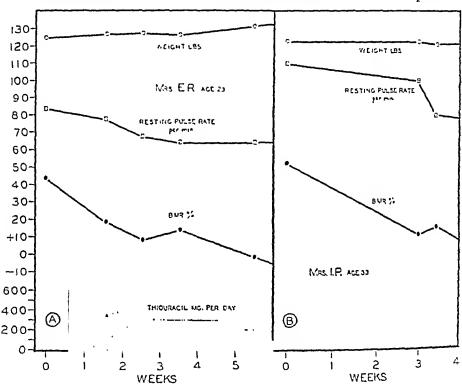
FIG. 1.—A. The response of a thyrotoxic patient to thiouracil.
B. The response of a thyrotoxic patient to bed rest without thiouracil.

thiouracil was prompt and dramatic. In addition to the decline of the B.M.R. and the pulse rate to standard normal values within three weeks and a gain in body weight of 10 lbs., the patient's thyrotoxic symptoms disappeared. No change in her daily routine as a house-wife and a mother accompanied this treatment and no other coincidental medication was given.

Fig. 1 B portrays the response of a goitrous patient with a similar elevation of the basal metabolic rate whose only treatment was bed rest in a hospital. The changes were rather similar in the two cases, but the symptomatic improvement was more pronounced in the patient who received the thiouracil.

It is a well-known fact that spontaneous remissions do occur in Graves' disease but unquestionable improvement follows therapy with

thiouracil with such regularity that the factor of spontaneity is probably of little consequence in determining the results. However, the possibility of the occurrence of natural regressions in the course of hyperthyroid disease, facilitated by rest, sedation and psychotherapy must not be overlooked in attempting to assess the clinical value of any so-called anti-thyroid medication.

THE DOSAGE OF THIOURACIL.—It is generally agreed that the optimal initial dose of thiouracil for adults should be 400 to 600 mgm. daily, depending upon the severity of the thyrotoxicosis. Smaller doses are likely to be ineffective and larger doses may be toxic. On account of the ease and rapidity with which thiouracil is excreted, the amount for the day should be administered in divided doses, for example, 200 mgm. at approximately eight-hour intervals.

At first, with a view to avoiding toxic reactions, the intake of the drug was reduced automatically at the end of one week to 500 mgm. per day, from an initial dose of 600 mgm. and, at the end of another week to 400 mgm., etc., but subsequent experience has shown that it is permissible, if not advisable, in the absence of obvious contra-indications, to continue the maximal conventional dose until clinical and metabolic improvement is evident.

The development of severe toxic reactions is most likely to occur during the first three weeks of the treatment and often irrespective of the dosage employed. It is at this time, therefore, that the patient should be observed most carefully. If this so-called " danger period " is surpassed without mishap there is less likelihood of alarming complications from intolerance to the drug subsequently, although no thiouracil-treated patient is immune from toxic side-effects at any time during the course of the treatment or even after the discontinuance of the drug.

If the dose be reduced too rapidly or discontinued before the remission is established, a relapse with a recurrence of the thyrotoxic symptoms is apt to occur.

Some clinicians have advocated a dosage schedule on a quantitative basis, claiming that approximately one day of treatment with 600 mgm. of thiouracil is required for each percentage of elevation of the basal metabolic rate to bring this within the normal range (Lahey et al., 1945). In other words, a drop of the B.M.R. at the rate of 1 per cent. per day is anticipated. While this is a simple guide which may be applicable in a majority of the cases, there is the danger, perhaps, that this system of calculation may entail an over-estimate of the time required to attain the optimal effects. It must be realised that definite manifestations of hypothyroidism and myxœdema can develop, with depression of the B.M.R. to very low levels, if the usual therapeutic dose of this drug be continued too long. I do not think that we are prepared at this stage to accept any rule of thumb pertaining to thiouracil therapy. Rather the treatment of each patient should be individualised with re-checks of the B.M.R. and the clinical status

at weekly or bi-weekly intervals, especially during the early phases
of the treatment, with regulation of the dosage in accordance with
the findings.

MODIFYING FACTORS.—The length of time required to accomplish
the desired effects depends upon several circumstances including the
nature of the thyroid disease, the severity of the thyrotoxicosis as
reflected by the initial height of the basal metabolic rate, the duration
of the hyperthyroidism, the size and character of the goitre and
pre-treatment with iodine.

While the response to thiouracil therapy often is satisfactory in
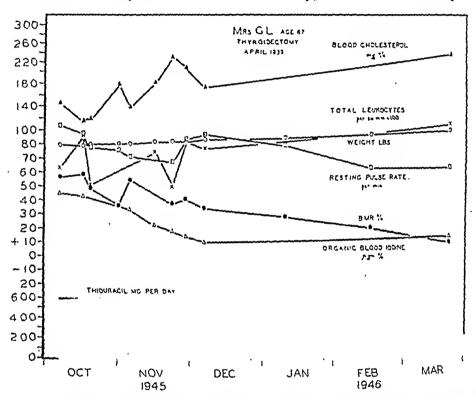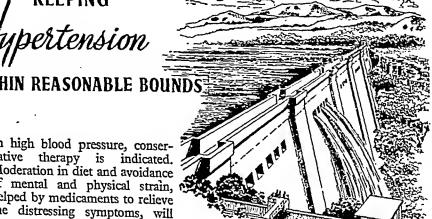
FIG. 2.—Showing the delayed response to thiouracil in a patient with post-operative recurrence
of hyperthyroidism, who had received Lugol's solution for one year prior to the thiouracil
therapy.

both primary hyperthyroidism or Graves' disease and nodular goitre
with hyperthyroidism, the observations indicate that the patients with
Graves' disease respond more readily and more completely than those
with so-called toxic adenomas. Apparently, the thyroid gland of
typical Graves' disease can be quickly depleted of its hormone and,
as a result, the hyperthyroidism is rapidly relieved but in the toxic
adenomatous goitre, wherein the acinar spaces are filled with colloid
containing a larger store of mobilisable hormone, the response is more
variable.

In general, those patients who have had thyrotoxicity of short
duration, i.e. three to six months, respond more rapidly than those
who have had the condition for a longer time. Also, in those patients

with large nodular toxic goitres, the response tends to be slower than in those with small or moderate diffuse goitres.

The greatest delay is observed in patients who have taken iodine for long periods of time immediately prior to the institution of the thiouracil therapy (Fig. 2). In such cases, the thyroid gland, presumably, is filled with hormone-containing colloid which must be expended before metabolic and clinical response to the thiouracil becomes manifest.

According to the degree of suppression of the hyperthyroidism and hypermetabolism, the dosage of thiouracil is decreased progressively
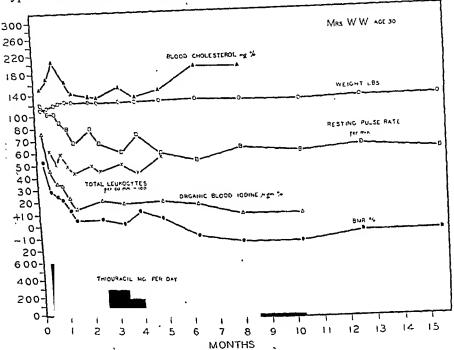
FIG. 3.—The characteristic effects of thiouracil in a patient with Graves' disease.

over a period of several weeks to the so-called maintenance level which is usually 100 or 50 mgm. per day. Evidences of undertreatment may necessitate the cautious upward readjustment of the dosage from time to time but the objective should be to utilise the smallest possible effective maintenance dose.

THERAPEUTIC RESPONSE

REMISSION OF THE HYPERTHYROIDISM.—After a patient's thyroid disturbance has been quiescent with a normal or subnormal B.M.R. for six to nine months during the last six to eight weeks of which time a maintenance dose of thiouracil has been effectual, the administration of the drug often can be stopped with a continuance of the remission (Fig. 3). How permanent these sustained remissions will be and

whether such patients may be regarded as " cured " are details which constitute the chief centre of interest in this field at the present time.

Degrees of improvement permitting the cessation of all anti-thyroid treatment have occurred in 20 of my 60 patients. The longest remission which I have observed so far has been fourteen months. Another patient has remained well with normal B.M.R., pulse rate and body weight for a period of thirteen months after stopping the drug ; another ten months ; still another eight months ; three have maintained their remissions for seven months ; three for five months and the remainder for two to four months. All of these individuals are still under observation.

In some cases, relapse follows discontinuance of the thiouracil especially if it is stopped before the full irreversible (?) anti-thyroid effect is established ; or a temporary recurrence of the thyrotoxicosis may be aggravated by emotional stress, physical strain or an acute infection. The beneficial effects of thiouracil, like those of thyroidectomy, are attributable to the interruption of a formidable cycle of unbalanced physiological processes. Neither method of treatment is directed toward the correction of the fundamental ætiology of the disease.

There is no such thing as thiouracil-escape or thiouracil-resistance comparable to the well-known state of iodine-resistance. Patients who are responsive to thiouracil can submit to successive courses of it with the expectation of equally good results. But a small percentage, probably in the neighbourhood of 5 per cent. of patients, are refractory to thiouracil for some reason which is unknown at present, even after adequate therapeutic trial and these must be classed as failures so far as lasting effects from medical management of this kind are concerned. There have been five such cases in my series all of which were examples of toxic nodular goitres or those regarded as mixed types. Such patients automatically become candidates for thyroidectomy.

THIOURACIL AND SURGERY.—Thiouracil has not supplanted and probably will not supplant the surgical treatment of goitre, except perhaps in certain selected cases. There is now no practical basis for the categorisation of patients into those who should be carried along on thiouracil therapy and those who should be subjected to operation. Actually, this entails the application of sound clinical judgment. No patient should be allowed to seriously harbor the impression that treatment with thiouracil is a sure and reliable substitute for surgery since the psychological implications of false hopes may embarrass the physician as well as the patient. However, the need for a hasty decision regarding operation usually does not prevail with the use of thiouracil and the question of surgery may be deferred, reasonably, pending the results of the chemotherapy.

Thiouracil is a valuable adjuvant to surgery. In some goitre clinics, apparently, thiouracil is used routinely for the pre-operative

preparation of patients. The advantage claimed for this practice is that the number of so-called dangerous risks is reduced ; the necessity for multiple-stage procedures is eliminated ; the occurrence of post-operative thyroid storms is avoided and the period of hospitalisation is minimised because the patient may be ambulatory during the period of pre-operative preparation. Further, the need for repeated operations may be evaded since most of the patients with persistent or recurrent hyperthyroidism appear to be readily controllable with thiouracil. Six of my cases were examples of post-operative recurrence of hyperthyroidism and, in all but one, the results were most gratifying.

I believe that most, if not all, toxic nodular goitres should be treated surgically not only because of the variability of their response to thiouracil but also on account of the potential growth hazards of such glands and their oft-times subtly baneful influence upon the cardiovascular system.

The reasons for the performance of subtotal thyroidectomy in 10 of the 60 cases included failure or undue delay of response to thiouracil, nodularity of the goitre, pressure symptoms due to enlargement of the gland under treatment and the development of toxic reactions to thiouracil. Lugol's solution was administered pre- and post-operatively with, usually, discontinuance of the thiouracil for one week prior to the surgical procedure. In all instances, the operative and immediate post-operative courses were extraordinarily smooth and uneventful.

THE BLOOD ORGANIC IODINE.—The so-called organic (protein-bound) iodine content of the blood is generally interpreted as an index of the amount of hormone elaborated by the thyroid gland and delivered to the circulation. The normal values for this blood constituent according to the method employed in the present investigation range from 8 to 12 micrograms per 100 c.c. of whole blood. A systematic study of the blood organic iodine was made in 43 of the patients. The pre-treatment values were consistently elevated from slightly above normal to 76 μgm. per 100 c.c. of blood. The administration of thiouracil brought about a decline of the blood iodine in 32 of these patients and in 11 there was little or no variation from the pre-treatment level.

Fig. 4 serves as a summary of the changes in the B.M.R., the blood organic iodine, the body weight and the pulse rate in 43 responsive patients over the first sixteen weeks of their treatment. While there is a considerable spread in some of the groups of observations due to the somewhat erratic behaviour of certain individuals, the various trends are suggested by the bunching of the curves with the formation of more or less distinctive patterns.

A certain correlation is evident between the decline of the B.M.R. and the reduction of the concentration of the organic iodine in the blood, indicating that the amount of hormone delivered to the blood stream by the thyroid actually is diminished as a result of the treatment. In some instances, the blood organic iodine returned to normal sooner than the B.M.R.

THE BLOOD CHOLESTEROL.—Owing to rather marked variations in the plasma cholesterol, this is not a reliable diagnostic or therapeutic guide since low, high and normal values are encountered before treatment. Often, however, a decided elevation of the plasma cholesterol content is observed after the beginning of therapy with thiouracil. Hypercholesterolæmia usually occurs when the basal metabolic rate becomes subnormal and thus is a manifestation of overdosage with onsetting myxœdema.

Of the 46 cases in which repeated estimations of the blood cholesterol
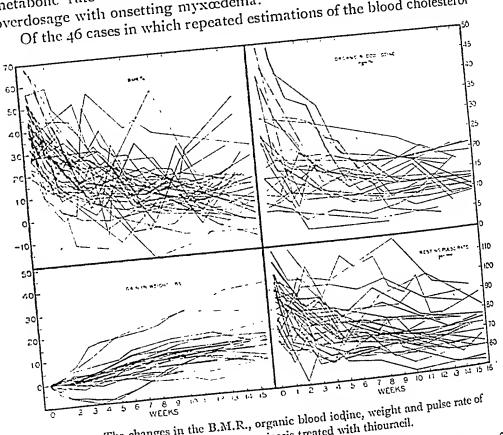
FIG. 4.—The changes in the B.M.R., organic blood iodine, weight and pulse rate of 43 patients with thyrotoxicosis treated with thiouracil.

were performed, a rise occurred in 36 following the exhibition of thiouracil.

CLINICAL CONSIDERATIONS.—Almost all of the patients exhibited a gradual increase of weight although the gain of weight was not pronounced during the first two or three weeks. Some patients even showed a drop in weight during this time followed by an increase subsequently.

In every instance the resting (basal) pulse rate decreased.

In a majority of instances, thiouracil exerts a beneficial influenc upon most of the clinical signs and symptoms of thyrotoxicosis. Th improvements in the subjective symptoms commonly associated wit the hyperthyroid state do not lend themselves to graphic representatio as do the data shown in the charts. However, the subjective chang are even more impressive, in some respects, than the objective one

In all of the responsive cases a return of well-being accompanied the subsidence of the hyperthyroidism. It is a common experience that within a few days after beginning the use of thiouracil, many of the patients are aware of a distinct clinical improvement. The time required for the establishment of the remissions, characterised by a normal B.M.R. and freedom from the usual manifestations referable to the thyrotoxicosis in patients who did not receive previous iodine medication, varied from one to fourteen weeks with a general average of thirty days. The average amount of thiouracil required to accomplish the result was 13 gm.

A slight to moderate increase in the size of the goitre is frequently observed during the early stage of treatment with thiouracil but, in many cases, after several months of maintenance therapy, the diffusely hyperplastic type of thyroid gland actually diminishes in size.

Changes in the exophthalmos are inconstant. Usually this sign does not increase and, in most instances, it becomes distinctly less obvious due perhaps to diminution of muscular spasm and lid lag.

THIOURACIL AND PREGNANCY

The possible effect of thiouracil on the progeny of thyrotoxic women treated with this drug during pregnancy is a question which deserves careful consideration. The experimental administration of thiouracil to pregnant rats was shown by Hughes (1944) and Goldsmith et al. (1945) to cause, by reason of placental or mammary transmission, hyperplasia of the thyroid gland and retarded development in the offspring. Enlargement of the thyroid glands of the newborn infants of thiouracil-treated mothers has been recorded (Eaton, 1945). In a recently reported instance of the death during the sixth month of pregnancy of a thyrotoxic woman while undergoing treatment with thiouracil, the thyroid gland of the fœtus was enlarged and hyperplastic, resembling the gland of an adult receiving too much thiouracil (Davis and Forbes, 1945).

Therefore, the utmost caution is indicated with respect to the use of thiouracil during pregnancy. That this state is not a contra-indication for thiouracil is shown by the fact that one patient took this substance throughout the whole course of gestation with marked benefit but without apparent ill effect whatsoever to herself or the child (Fig. 5). No obvious enlargement of the infant's thyroid gland was detectable. Another patient delivered a normal baby at term after having taken thiouracil since the sixth month of pregnancy. Still another is approaching term in a satisfactory condition of health, having used the drug since the second month of pregnancy. It is advisable, probably, to adjust the dosage during pregnancy so that the basal metabolic rate remains near the upper range of the normal rather than lower, especially during the later months of gestation.

In view of the reputed high concentration of thiouracil in the

of their possible prophylactic action against neutropœnia during thiouracil therapy but their value in this regard has not been affirmed. In the event that agranulocytosis does develop, the thiouracil should be discontinued immediately and reliance placed in the liberal use of penicillin. The use of the sulphonamide compounds should be avoided. The granulocytopœnia *per se* is not necessarily fatal, rather it is the superadded infection which is life-endangering.

Newer Thiouracil Compounds

It has been found that the toxicity as well as the antithyroid potency of thiouracil may be altered by changing the chemical structure of the molecule. Already several thiouracil derivatives have been tested clinically. Of these propyl thiouracil and ethyl thiouracil appear to be the most promising. According to Astwood (1945), who has had considerable experience with many different compounds of this type, propyl and ethyl thiouracil are approximately five times as active in man as thiouracil and exhibit a lessened tendency to the production of undesirable side effects.

To date, I have had an opportunity to treat only seven patients by means of propyl thiouracil. The usual dosage for the induction phase of the treatment is 75 mgm. per day, *i.e.* 25 mgm. at approximately eight-hour intervals. In agreement with Astwood's original observations, the clinical results have been satisfactory but the response is somewhat slower than with the use of thiouracil.

The Mode of Action of Thiouracil

If one studies the histological appearance of a thyroid gland before and after treatment with thiouracil some interesting details will be observed. It appears that under thiouracil therapy the hyperplastic thyroid of Graves' disease becomes still more hyperplastic, yet the production and the outpouring of thyroxine by the gland is diminished. How can this paradox be explained ? Apparently, thiouracil causes an interference with the elaboration of thyroxine by the thyroid tissue by preventing the utilisation of iodine. This is thought to be mediated by the suppression of certain enzyme systems which are necessary for the synthesis of the hormone from its iodine-containing precursors.

The extraordinary hyperplasia of the thyroid gland which follows the administration of thiouracil is probably the result of the excessive, unopposed production of the thyroid-stimulating hormone (thyrotropin) by the anterior pituitary in response to a lowered level of the thyroid hormone in the blood. Under these circumstances, an inverse relationship exists between the anatomical and the physiological status of the thyroid gland, *i.e.* increased cellular hyperplasia with decreased secretory function.

Notwithstanding the blockage to the collection of iodine within

the thyroid, iodine will still bring about involution of the gland in the thiouracilised subject. This is significant with reference to the practice of prescribing supplementary iodine medication pre-operatively with a view to increasing the consistency of the organ and reducing its vascularity, thus decreasing some of the technical difficulties of thyroidectomy.

In spite of plausible theories, the exact mode of action of thiouracil and similar compounds in modifying the structure and function of the thyroid gland is still open to question and awaits final decision.

The Effects of Thiouracil upon Secondary and Non-Hyperthyroid Conditions

The beneficial effect of thiouracil in causing the amelioration of certain conditions aggravated by or associated with the thyrotoxicosis and hypermetabolism, such as cardiac irregularity and incompetence, diabetes mellitus and psychotic manifestations can be rather striking, as noted in print repeatedly.

Thiouracil probably is of no definite value in conditions not associated with hyperthyroidism. The use of this drug for the relief of angina pectoris was a natural sequel to the not too popular method of treating this complaint by means of thyroidectomy. Some benefit has been reported resulting from thiouracil therapy in patients with angina pectoris, especially those with elevation of the B.M.R. (Raab, 1945). It has been suggested by Wastl (1945) that certain of the thiourea derivatives might be beneficial in the treatment of vascular hypertension.

Summary

1. A favourable response to thiouracil therapy can be expected in approximately 80 per cent. of the patients with hyperthyroidism.

2. Thiouracil may be used to advantage under the following circumstances : (a) In hyperthyroid patients with diffuse goitres in the hope of initiating a prolonged and ultimately permanent remission of the hyperthyroidism ; (b) In patients with mild or recurrent hyperthyroidism ; (c) In patients with conditions unfavourable for surgical operation ; and (d) Preparatory to thyroidectomy with a view to minimising the element of operative risk.

3. Unpredictable toxic effects such as agranulocytosis, although relatively uncommon, should be anticipated, recognised early and dealt with promptly.

4. The expectation of newer, more potent and safer antithyroid chemical compounds for clinical use can be entertained.

5. All statements pertaining to the therapeutic efficacy of thiouracil must be regarded as tentative pending the results of more accumulated experience with this type of drug.

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TRAUMA AND THE NERVOUS SYSTEM *

WITH PARTICULAR REFERENCE TO COMPENSATION AND THE DIFFICULTIES OF INTERPRETING THE FACTS

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INTRODUCTION.—For many years in hospital and private practice one has become increasingly conscious of the importance of this subject to the patient and to his doctor, to the specialist and to the lawyer all in their different roles. During the war experience in many respects became more crystallised, and it is my purpose to explain some of the problems with which one has been confronted in the hope thereby of stimulating interest.

How much is it given to anyone to know what is in another man's mind ? This question obtrudes itself repeatedly in one form or another in the experience of all clinicians when faced with the evaluation of an illness, or confronted in court by the opposing counsel. So many of our views are purely a matter of opinion, but fortunate indeed that it is so since, if medicine was an exact science, it would be an unpleasant if not intolerable profession. Facts there are in abundance, indisputable and defensible although frequently open to a variety of interpretations, or more correctly misinterpretations, a circumstance that makes us beloved if not necessarily admired by the lawyer and the journalist, with the one for the joy of litigation, his *raison d'être*, with the other for the constant supply of spicey copy, his bread of life. It is pertinent to ask ourselves up to what point we do practice an exact science and beyond that mark how do we handle the art. Clearly there are many sets of circumstances which are capable of only one interpretation, in each all must be agreed, a patient has a cold in the nose, a cyclist falls and breaks his leg, a person is blind or deaf. These things are obvious to the tyro no less than to the expert, but a more difficult elucidation requires knowledge and experience, factors which come with interest and opportunity, a sliding scale of value that by no means depends only on exertion. It involves the quality of competence. A sharpened wit may rapidly furnish an explanation for obscure aspects of the case which convince some but perplex others. Who are convinced and who are not ? Is it a matter of preference only ?—or is it preference based on reasonableness, a reasoned preference for what is attractive ? The process of thought when broken up into its components leaves nothing to be explained. This is, it seems, the crux of the matter. The expert witness by accepted usage is one whose expertness is in direct ratio to his knowledge and

the facility with which he expounds his facts and avoids confusion with theories. Thus always there are degrees, the element which brings out the personal equation and confounds the critics by its very persuasiveness. This, however, is subject to a test—the test of time, a salutary experience for those who approach their task conscientiously, but too often overlooked by others who refuse obstinately to learn their lessons. Would we do and say the same again is a recurring question, but too often the complacent answer is affirmative, bringing consolation to the doubting mind. Is it surprising that we grope so much in the darkness when the technique of satisfaction brings its inevitable reward of solace ?

Few of us have much training in court work. It is avoided by the young doctor through fear, and shunned by the older on the plea of insufficient time, and yet in the mind of both is the haunting thought that his ignorance may be exposed to ridicule, a healthy sign in so far as it indicates a realisation of limitation, but none the less it is a serious omission since each appearance is a yardstick by which can be measured the ability of clear thinking and honest deduction, an opportunity which no other part of our work affords. In the last resort a situation should be created for each problem with which we are confronted in order that zeal and prejudice do not mask the facts of the case. Such an attitude of mind at once separates the honest practitioner from the unscrupulous quack and charlatan who have far too long enjoyed a vogue and the doubtful advantage of material gain at' the expense of a credulous and unwary public. That it cannot continue is obvious to anyone who stops to ponder the trend of nationalisation and its effects upon those who exploit the mental and physical weakness of their fellow men. Let us beware lest we ever stoop to imitate this undesirable character.

Patients inevitably feel a bias in favour of trauma as the important factor in explaining the causation of any ailment which is not readily accountable for otherwise ; and understandably nervous manifestations fall prominently into this category, since even now many of them are imperfectly understood let alone satisfactorily accounted for in lay language. An infection may seem clear cut, a meningitis, a polio-myelitis ; yet so often an attendant fall seems inseparable to the patient's friends from the sequence of events, indeed so convincing a factor that often skilful arguments leave a doubt. A doubt in part due to our own uncertainty in many instances. Need we be so uncertain ?—or is it merely a desire to be scrupulously fair, fair that is to the individual for whom a favourable medical opinion may mean a reward in cash, commonly called compensation. A study of nervous infection is pertinent now that more is known of the mechanism whereby a virus acts, and the realisation that this variety of disease at least is self limiting. For example in poliomyelitis during an epidemic only a proportion of the victims develop the disease in an indisputable form ; others, although undoubtedly affected by inference

from all the circumstances, yet recover completely owing to some unrecognised resistance which allows a general reaction to stop short of calamitous paralysis. This must be a process dependent upon inherent factors of constitution and well-being favourable and unfavourable, but also influenced by matters external of which who can say that trauma is not one. While the virus is exerting its evil influence and the patient is little if at all affected, there must be a point at which the outcome is in doubt and at which the outside effects are all important for good or bad. Thus if we imagine these points in the process at any one of which an accident, less or more, may occur, its results manifestly will differ according to the timing—little or nothing if early or late but overwhelming should it happen when the natural process is in doubt. We cannot escape the complexity of this problem, and nothing but added confusion accrues from attempting to simplify it. One solution would be to allow that any accident at any time during the accepted incubation period was held responsible, but that could never be allowed since clearly it would open the door to a greater degree of unscrupulous evidence than exists at present. A fair and more honest attitude is to state the facts clearly, a matter by no means as easy and simple as it sounds, and to leave it to others to make the judgment.

The illustration of poliomyelitis is not peculiar, the principles implied being equally applicable to a wide range of conditions, many much more common if less dramatic, including almost all forms of neuritis, brachial, sciatica and the rest.

Sometimes, indeed often, one despairs of litigation. It is endless and often unsatisfactory, but so too are examination tests which have been in vogue for a much longer time and always had their critics, yet remained unreplaced for want of a better system. So it is with litigation, the real pity being that it has become increasingly wrapped up with finance. One reflects with wonder at the consternation of the legislators *circa* 1897 could they but have had a peep of the outcome through half a century of the laws they were formulating. It is appropriate to consider briefly some aspects of the Workman's Compensation Act in its evolution and what it has come to imply in medicine to-day. Familiarity has led to indiffernece, and most of us are ignorant of how far the Acts have been extended and are still extending. The present position certainly affords material for reflection. Quoting Sir John Collie,[3] it was calculated by the Home Office, in affording information as to the probable effect of the passing of the Act of 1897, that 150,000 accidents a year would fall within its scope. But in the seven principal industries for which accurate statistics are obtainable, the number of cases of accident in which compensation under the present Act was paid in 1930 amounted to 461,130; in addition there were 2303 uninsured employers who reported that they were paying compensation in respect of accidents sustained by their employees.

Making due allowance for the extensions made by the subsequent Acts, and the possible increase in the numbers employed, the disparity between anticipation and realisation is striking. It leads to the conclusion, either that the framers of the estimate had been unduly optimistic and badly informed, or that they had failed to attach sufficient importance to the psychological and other effects of the passing of such legislation. Given in figures the comparison between then and now is not a question of an increase of thousands of cases but of hundreds of thousands, and not a question of tens of thousands of pounds but of millions.

What are the reasons for the large number of cases now coming under the Workman's Compensation Act? An undoubted one, pertinent to my subject, is that whereas in the original Act no consideration was given to disease, a constant chain has been linked ever since by the accumulated results of Court cases which pass into law an ever increasing range of possibilities. Altered conditions too are playing their part; for instance there has been a great increase in mechanisation, and processes have been considerably speeded up, which might be alleged to cause more casualties. On the other hand, of 113,249 accidents recorded some years ago before the war, the majority were due to some failure in the human element and not to the machinery. There have been increased Statutory and other provisions framed to avoid accidents, and many operations are now safely performed by machinery which in the past were done by manual labour and put an enormous strain on the workmen engaged, rendering them liable to hurt. Probably, too, some of the increased number of accidents are due to the carelessness and slackness which some observers have noticed among many of the younger generation of workers. The door of compensation being once opened it has since received so many pushes from the Legislator and the Bench in interpreting what is understood to be the intention of the Acts, that it is now almost as wide open as even the extremists could desire.

TRAUMA IN ORGANIC NERVOUS DISEASE

The approach to the organic side of this subject is perhaps best made by selecting in series a few of the more familiar conditions and bringing out the essential points as they arise.

DISSEMINATED SCLEROSIS.—During the hundred years or more since disseminated sclerosis was first recognised as a pathological entity, the question of trauma keeps cropping up among the etiological factors as indeed it must always do in any organic disease whose elucidation proves difficult. Even before Charcot's wonderful description of the symptomatology and pathology of this condition an interesting paper by Leyden in 1863 emphasised the causal importance of trauma while linking to it damp and cold, mental stress and possible preceding infections. But by the start of this century the opinion was established that the principal change was a neuroglial

hyperplasia, and when pathological research was aided by new staining methods revealing more precisely neuroglial reactions it became customary to regard disseminated sclerosis as an infective disease. However, in spite of the enormous volume of work done in the hunt for a causal agent, no proof has been forthcoming, and this notwithstanding our greatly increased knowledge of virus and other infective processes which show many clinical features of a similar kind.

All through this long time theories of the relationship of accident have had their adherents, slightly so in the matter of causation, but more persistently in regard to aggravation, a question of prime importance in a malady which is prone to run so erratic a course of ups and downs, remissions and exacerbations. Quite obviously the distribution and incidence which has been carefully worked out statistically reveals an overall feature in geographical and racial incidence which precludes so chance a cause as accident as a prime factor. For instance, the disease is very common in Switzerland, whereas in the United States it is much lower than in Britain. Indeed outside Europe it seems to be rare. The geographical distribution can be carried further and in many instances pinned down to actual towns and localities. I remember well many years ago in the outpatient department of Professor Bing in Basle marvelling at the enormous number of these cases and learning from him that 3 or 4 out of every 5 patients with organic nervous trouble suffered from disseminated sclerosis. Again at one time the belief was widely held in this country and elsewhere that farm workers were especially prone. Such an idea, long disproved, is merely mentioned to show that environment and occupation in addition to racial distribution have attracted attention of workers in this perplexing field ; also examples of familial tendency are fairly numerous in the literature and is now unquestioned.

These reasons, very briefly mentioned, are perhaps chief among those which account for so little attention being given nowadays to trauma as a predisposing cause of disseminated sclerosis. No one aware of the facts would be likely to claim that trauma was essential or even common, but equally it is certain that in an individual case its consideration demands the most careful scrutiny and application of reason to all the known facts, clinical and otherwise. It would be rash to deny the possibility of a causal relationship between trauma and disseminated sclerosis and perhaps equally rash to assert it, as witness this example :—

Female (40). Fell seven years ago, damaging right hip but breaking no bones. Never walked without stick and great difficulty thereafter. Always assumed by herself and everybody else to be due to accident, but examination only recently showed indisputable signs of disseminated sclerosis including pale discs, nystagmus, and an upgoing toe on both sides, the opposite as well as the injured. The injured leg muscles extremely stiff, but great limitation of movement at all joints (disuse).

This case brings out the following points : (*a*) Did the patient have disseminated sclerosis at the time of the accident ?   (*b*) Was the accident a predisposing factor ?   (*c*) Was it a coincidence ?   Clearly from the facts at least it can be assumed that one was merged with the other, since the accident was wrongly presumed to have caused so much incapacity.   But equally it is thought to be inconceivable that peripheral trauma could by itself bring about such widespread central nervous change.   Then did it " light up " a latent tendency ?   Here it is that we come to the core of the problem in this important disease.

In this connection the following case is of interest :—

J. F. (34).   Diagnosed as disseminated sclerosis in 1936, quiescent until 1943 when an attack of dysentry (Sonne) aggravated symptoms for a time but never sufficiently to prevent him travelling to and from his work as a clerk each day, until January 1945 when a bus he was mounting started unexpectedly, throwing him to the ground.   He was dazed and bruised around one eye but managed with aid to mount the stair to his house.   After a day or two complete paralysis of the legs and much incapacity of the arms with general aggravation of all signs was manifest to the extent that he became completely incapacitated and is unlikely to leave his house again let alone follow a useful occupation.

In this case the relationship of trauma to the original illness cannot be in dispute, the onset having preceded the accident by many years, but obviously it is more than a coincidence that complete incapacity resulted at once so strikingly that a jury must be convinced of the connection.   Indeed in this case the substantial claim was settled out of court.   But we are interested more than merely in the application of lay reasoning to circumstantial evidence.   What did happen to stimulate the pathological process in this man ?   Could it be that the disturbance broke down in some way the defensive immunity he had acquired by altering his state of nervous tension to the extent that the process became irreversible ?   or was it the actual bang of his fall that directly damaged nervous tissue ?   While preferring the former choice one is yet left unsure.

For over a hundred years a great deal has been written about the traumatic etiology of disseminated sclerosis.   There can be no question that a number of cases have developed shortly after trauma.   Wilson[8] states that the concept of a blow on the arm causing multiple plaques is untenable.   But if emboli were proved to be the cause of the sclerotic plaques the statement would no longer be valid.

J. M. Neilson[7] quotes the case, similar to the one above, of a fireman who slipped down a long flight of stairs in a sitting posture, receiving thus fourteen bumps which jarred the spine.   He appeared two weeks later with a fully developed picture of disseminated sclerosis, and averred that he was perfectly well before the accident.

The interpretation of this case as of nearly all, if not all, cases of related trauma and multiple sclerosis, is that the jarring may crystallise

or precipitate the disease but cannot actually cause it. Some authorities state that any acute disorder seems capable of starting the disease, but others deny the relationship. Until the cause of disseminated sclerosis is known and the pathogenesis understood, such discussion is largely devoid of meaning.

The medico-legal aspects of this difficult question can only be judged in each individual case. Russell Brain [2] enumerated the following possibilities for consideration :—

1. That the association is a coincidence.

2. That traumatic lesions of the nervous system may be mistaken for disseminated sclerosis.

3. That trauma may induce changes in the neighbourhood of pre-existing, but hitherto latent, plaques of disseminated sclerosis and so lead to the appearance of symptoms.

4. That a patient, after spending some time in bed as a result of the trauma, may manifest symptoms because he has lost the power to compensate for a defect, such an incoordination of the lower limbs due to a previously acquired disseminated sclerosis.

5. That the trauma (e.g. a fall) may be the result of pre-existing symptoms of disseminated sclerosis (e.g. incoordination).

6. That the trauma may produce a lesion of the nervous system (e.g. contusion) which may afford a locus minoris resistentiæ for the development of the virus of the disease, hitherto latent.

War experience might have been expected to afford some light, especially since the age group involved coincides closely with those most liable. During one period when the medical admissions to my hospital numbered upwards of 20,000 only 8 cases were diagnosed as disseminated sclerosis, and in only two of these was the question of trauma sufficiently obvious to be considered, although even then their experience was no worse than that of their immediate associates. And in one a pale disc proved that the incident occurred during the course of a previously existing disease. The subject was discussed at a clinical meeting attended by over seventy medical officers when no expression of opinion shed any very different light. A possible factor but not a cause.

EPILEPSY.—Of all conditions in which the role of trauma has been contested most hotly this is the one *par excellence*. Here cause and effect appear to be related most significantly in time and in space, a view-point which inevitably will impress almost all juries, especially those members who most fancy their ability to make logical conclusions. A young man hits his head or is struck ; the degree of violence varying from trivial to serious, and at a later date, after often months or even years, takes his first convulsion. The two are linked together and thereafter the label traumatic epilepsy is affixed with the result that

on electroencephalographic examination. The practical aspects of this in connection with prevention are fairly obvious.

Proof of Hughlings Jackson's definition of epilepsy as a sudden excessive unruly discharge of neuronal cells had to await the patient labour of Hans Berger who, in 1929, published the first electro-encephalograms. Much useful work has since been done chiefly in comparing brain records of patients with supposedly healthy persons and the Gibbs have produced a valuable classification of electro-encephalograms which make it possible to envisage a time when the use of this apparatus will be demanded in all disputes concerning cause and effect in epilepsy. It may never offset the hard facts of legal logic completely, but it should and will influence the amount of compensation awarded.

In my view one may summarise the situation by stating categorically that trauma can only cause symptomatic epilepsy by creating gross demonstrable cerebral damage, and even thus it is quite probable that newer methods will lay bare some inherent genetic fault, otherwise how is one to explain that in a series of over 200 head wounds consecutively observed by myself in only two did convulsions occur within the first two weeks of wounding. Those not susceptible may have no fits although it is well known that their behaviour in other respects may be greatly altered and their use of even moderate quantities of alcohol may be pathetically grim in its results.

PARKINSONISM.—The spate of literature which accumulated after the advent of epidemic encephalitis contains a sprinkling of references to the possible association of trauma to the production especially of the common sequel of Parkinsonism. There were advocates both for and against, but always doubts persisted, which were expressed by Kulkov [5] in the question : " Could it really be the fact that a cranial trauma by way of destruction of tissues or in consequence of haemorrhages in the region of paleostriatum (globus pallidus) or adjacent apparatus, could evoke a vivid picture of Parkinsonian appearances ? "

Since Parkinsonism is a syndrome having various etiologies (such as encephalitis, syphilis, arterio-sclerosis) we can take it for granted that the disease may appear after a trauma which calls forth some very subtle and elective haemorrhage around which later secondary symptoms of neuroglial sclerosis would arise.

According to Jelliffe and White, " trauma may be a sufficiently exciting cause to bring the symptoms of a slumbering paralysis to the surface, or those of a mild case rapidly to a severe stage." Emotional disturbances undoubtedly play a large role in causing the arterio-sclerotic foundation. The direct relation of the striatum to emotional activities should be borne in mind. One patient in whom I have watched the slowly advancing development of paralysis agitans for upwards of ten years believes even now that her incapacity originated as a result of a painful venesection for transfusion during a debilitated

state after operation. In this case as in others one has seen it happen that tremor commenced in the injured limb. On the face of it even the lay imagination has to be much stretched to accept this association ; moreover the claimant in law would have a poor chance of establishing a case. Yet are we really so sure of its impossibility ? Bing [1] coined a phrase, " Commotional encephalos," to suggest a disturbance of function, short of a demonstrable pathological lesion, that would be sufficient to set the stage in a debilitated and frightened person for rapid advancement of a latent arteriosclerotic process. How much more understandable the " lighting up " of a dormant encephalitis, since it is well known that only a proportion (possibly 25 per cent.) of those who used to be seen with acute encephalitis proceeded to the Parkinson state after a very variable interval, often indeed only those in whom the acute phase was only detected in retrospect ; the remainder apparently making a complete recovery.

Continental authors on the whole have been much more particular in mustering their evidence than we are, to the extent of often laying down rules by which a given case must be measured if the relationship with trauma is to be accepted. For instance Bing advances the following points in order to establish a causal connection between the trauma and paralysis agitans :—

(1) The trauma must be severe enough to be able to cause some cranial lesion or at least call forth symptoms of a *commotio cerebri*.

(2) The patient who suffered from the trauma must not have been previously subject to any cerebral symptoms.

(3) The Parkinsonian symptoms must not follow immediately from the trauma ; their development ought to be preceded by some prodromal symptoms (cerebral symptoms) which would then gradually develop a characteristic picture.

TRAUMA IN PROVEN CONDITIONS

There is no difficulty in selecting the symptom-complex of herniated intervertebral disc as a condition in which the link between injury and resulting neurological state is indisputable, differing only in degree and kind from a hemiplegia resulting from gross damage to a part of the brain, the essential difference being that the violence (often even trivial) is indirect. This fact may be important since it introduces the principle that the outward effect of trauma may be invisible and established solely from the inference drawn from history and physical examination. Twenty years ago, before the herniated disc complex had been explained and accepted, it is inconceivable that a simple jerk or stubbing of the foot would ever have been invoked to explain a sciatic pain, yet obviously many victims must have continued in ignorance of the role trauma had played in their malady, content to believe that a mysterious neuritis accounted for their pain

and suffer the indignity of teeth extraction and other measures designed
to eradicate septic foci.   Unhappily now authors try to oversimplify
this problem by attempting to use this simple pathology to explain
all manner of cases.   But nature is not interested in simplicity, and
in this condition our real challenge remains, which is to discover the
true relationship between disc pressure and neuritis, since it is already
agreed that in many instances the two exist side by side.   Progress
has naturally been slow in revealing the pathologic appearance of
painful nerves as seldom is material available for examination, but
now very many cases have undergone operation when it is frequently
found that the compressed roots are thickened, congested and inflamed.
An association that requires no septic or toxic theory to explain.   We
must beware of being too dogmatic lest we open up too attractive
a field for litigation, and yet the implications of all this are far reaching
in connection not only with sciatica but of " neuritis " in many other
parts of the body, a subject which for long has been in an unsatisfactory
state, dearly loved by the quack who finds in it a rich and safe field
for his universal technique.

The multiplicity of pathological lesions which affect the spinal cord
itself are all well recognised entities whose behaviour conforms in
each case to a definite process whether it be inflammatory, vascular,
or neoplastic, and yet it is the experience of all practitioners no less
than specialists that violence less or more is presented by the victim
or his friends as the alleged explanation.   Numerous illustrations of
this leap to one's mind.

A middle-aged lady with chronic lumbago secretly visited a chiropracter
and was submitted to the common if unorthodox procedure of powerful blows
on the spinal column while lying prone on a table, the middle portion of which
was missing.   Returning home with difficulty she retired to bed and never
rose again.   Fearful of her doctor's censure she lay for some weeks before
obtaining help, but soon, by the ordered methods of diagnosis, it was found
that a comminuted fracture had occurred at the site of a metastatic growth.

This illustrates quite vividly that things are not always what they
seem to be, and so in every instance of spinal cord disease pathology
must go relentlessly on, its existence brought to light by injury or
violence, often aggravated but surely never initiated.   But now the
law of compensation has reached the point through a long series of
litigation claims when the chances of success in law are strong if it
can be proved that on a given date immediately before an accident
the patient was symptomless and normal on examination ; that violence
was indisputable even if variable in degree, and preferably shown by
the same medical witness that physical signs began and progressed
from a brief time after the injury.

A recent instance of this happened to a gamekeeper aged 60 who was
penned between a backing car and a brick wall, bruising but not fracturing
his pelvis.   He had been active and well before this but during the few days

while recovering from his bruises, one foot, that on the injured side, was found to be weak. From this moment the clinical picture has developed into the easily recognised one of amyotrophic lateral sclerosis.

Dare we say that the accident had nothing to do with the subsequent condition ? I think not, and for this reason ; the sequence of events reach a logical conclusion especially in the lay mind, and moreover we are dealing with a malady whose etiology is unknown, differing in that respect from the surer ground of established causes as in meningitis, poliomyelitis and the rest, where the reasoning even allows for a prodromal phase of several days, and each case follows a recognisable behaviour pattern.

How different is the picture in the young boy who was admitted a few weeks ago with severe headache and vomiting after hitting his head sharply against an iron girder. This youth was in the second stage of tuberculous meningitis and died eight days later, showing that the accident was an unimportant incident.

Carrying the argument further, it is seen that when the whole course of the disease is known as an entity we are medically strong, and conversely when much is still doubtful or uncertain we are weak. None the less in spite of this appeal to reasonableness and the hunting down of simple but significant facts, it is safe to assume that much time and energy will be spent by the unwary in making impossible claims ; a kind of projection of theory over fact from whose occasional success springs continuing hope. Too often an ignorant doctor with a plausible manner gives an opinion that will override the more cautious utterances of the scientific specialist.

Since early times the association between brain tumour and injury has occupied attention for reasons that are too obvious to require emphasis. Before the advent of neurosurgery and the experience clinically and pathologically of two world wars, it was a matter that once suggested must have been extremely difficult to disprove. However, nowadays the most that can be said is that head injury may be an incident in new growths within the skull just as indeed it may not be. An early case showing this remains in my mind after many years.

The patient, a young man of about 30, was under observation for epilepsy which had developed after a car accident. No fracture or obvious damage was found in the skull and no organic signs, but it was noticed that the fits had a Jacksonian quality. However, they were infrequent and he returned home to take the usual sedatives. He was admitted to the same ward some five years later, having fallen unconscious in the street. Death followed and at the post-mortem two gliomata were found, one small and slow growing, in the motor area corresponding to the fits, the other near the corpus collosum into which a large hæmorrhage had occurred. Even if it was allowed that the accident had caused the one glioma, it is inconceivable that the second could have had any association. Therefore if one had not, why should the other ?

Again reciting war experience, it is highly probable that if trauma had any true relationship with cerebral tumour such an association would have emerged in an incontroversial way among the many head wounds and injuries of every variety and degree. All evidence points entirely the other way even now when much follow-up material is available. The proportion of brain tumours in the army was small in all campaigns and in my own experience the contribution of the front line soldier was infinitesimal. I cannot give figures in an overall sense, but in a concentrated sample one remains impressed with the complete absence of any hint that neoplastic pathology was influenced by violence—gliosis there may have been, but glioma never, one being compatible with continuing life, the other not.

On the other hand vascular disturbance in the skull is common, with its consequent effect on nerve function. Personality changes following severe concussion are regular examples of this, also every variety of catastrophe from a ruptured aneurysm to a delayed subdural hæmatoma is familiar in war as in civilian practice, but here it is important to recognise that violence creates a situation by itself and does not play a part in initiating a pathological process that is understood. An analogy with cardiological knowledge is appropriate since in this field the effect of blows on the chest have been studied with great care. It has been shown convincingly that even in the absence of external bruising or fractured ribs the myocardium may be profoundly disturbed and results including coronary thrombosis, arrhythmia, ventricular rupture and angina pectoris are accepted on occasion as due to this cause. The phrase " inefficient heart " is sometimes used to express the result accruing from a compression or blow over the precordium. Litigation is incessant in these matters with its tedious argument, but luckily up till now I am unaware of any claimant having the temerity to press his " inefficient brain," unaided by substantial additional signs, as the sole result of injury. Yet if allowed in one organ, why not in the other ?—the important point being that the effect of trauma is vascular and in that sense not a pathological process.

Leaving this subject to pursue a much more controversial question with a vascular slant, I should like to touch for a moment on these difficult and little understood cases of " burning pain " or causalgia. The wretched victims of this suffer agony which is often both mental and physical, due to the condition sometimes being unrecognised for what it is with insulting psychological treatment employed and the fact that the pain is very real.

An elderly miner had his left foot pinned by a fall of heavy stone. The skin was unbroken but extensive bruising resulted, although no bones were damaged as shown by X-ray. Very shortly even the signs of bruising disappeared, but gradually he complained of increasing pain on certain movements of the foot and in time he stated that he could not bear the weight of the bedclothes or a soft slipper unless the foot was swathed in wool. When

I saw him six months later this condition was unchanged and he was indignant at what he felt were the insinuations implied by the treatment he had received. This man was a good type and an excellent witness, giving his story in a convincing way to the extent of volunteering the statement that he felt if his foot was removed he would be as fit and happy as ever he had been. Most of the foot was tender to touch but there were trigger points which caused excruciating pain and a strenuous attempt to draw the foot away.

Numerous similar cases are familiar to anyone who has had the opportunity of studying the diverse effects of injury to a limb.

Since the sixties of last century this subject has intrigued neurologists and physiologists. In more modern times the names of Henry Head and Sharpey Schafer are identified with personal experiment in attempting its elucidation. Even now it is not fully understood, although the relationship between cause and effect is never in dispute, only the exact mechanism is in doubt. The answer, when worked out as it will be, may well give a far reaching clue to the role of trauma.

If we allow, as we should, that trauma of a peripheral nerve may disturb capillary circulation, allowing the vasomotor disturbances which take place in cutaneous areas deprived of sensation, then we are entering on an unpredictable phase of values. But it seems especially probable that the obscure inter-relationship of the vascular and nervous systems may be unravelled to the extent that injury has a precise and definable position among the etiological causes.

SUMMARY OF ORGANIC ASPECTS.—The examples I have chosen, although by no means exhausting the possibilities, do at least illustrate vividly how troublesome is the ground in attempting with any degree of exactness to evaluate the role of trauma in the etiology of organic nervous disease. One recognises only too clearly the difficulties of offering a convincing argument for or against in a given case, but none the less certain principles do shine throughout, not the simplest of which is the need for exactness of observation, which precept embraces the rule that the medical witness, be he expert or other, must never lower his standard to that of a partisan. The obviously ill-considered and biassed opinion does infinitely greater harm than mere ignorance to injure the age long and mutual respect of our sister profession— the law. As medical men we believe in the doctrine of specific causes, but with trauma one has to endeavour to get some general principles on which to go.

TRAUMA IN FUNCTIONAL NERVOUS DISEASE

There will be those who consider that this part of my subject should have been dealt with first, in that it is obviously the most difficult and most chaotic. I was tempted to do so but refrained on finding myself bewildered in the effort to find a single satisfactory line of approach. It is a crowded, tricky field to survey without

proper aid from accepted terminology, and with the years comes the realisation that experience is fallacious and judgment difficult, leading us to recognise that in medicine the area in which confident knowledge is at present possible is but a limited one. In the neuroses, especially the traumatic ones, final and absolute truth is not attainable, only working truth. To elaborate this a little further, one of the commonest mining accidents sheds much light. A fall of stone from the roof on to the working-man's back is, sadly enough, a very usual experience as I have good reason to know after a long association with the Scottish Mine Owners' Defence Association. The results of such an accident may best be thought of as a scale, at one end of which is the man whose spinal cord is irreparably damaged with all the attendant motor, sensory, reflex, and bladder changes. At the other end of the scale is the lucky man who by good fortune escapes with minor bruising from which he rapidly recovers. Between these two is every degree of symptom-sign combination. There comes a point on this scale when no sign, as we understand the term, is found and yet complaint is made. It is reasonable to argue that very slightly more damage would have produced some organic indication on examination. Let us admit at once that a limited amount of spinal cord disturbance may be impossible to detect clinically, but in what category is such a case to be considered ? Is it a slight spinal concussion or a traumatic neurosis ? From my experience with miners and the more concentrated opportunities of making observation during the war, I believe that the correct designation only becomes apparent at some interval after the event. A slight spinal concussion will recover completely in a short time, whereas a traumatic spinal neurosis will be perpetuated and possibly increased for many months depending on other factors both conscious and unconscious in the individual. It is these factors that I wish now to consider.

To turn to the dictionary is almost a digression, but in this connection it is helpful if the derivation is backed by acceptance and usage. The word " neurosis " in Greek means " nerve." In such a reputable publication as the American *Illustrated Medical Dictionary*, edited by Newman Dorland, an accepted authority, this simple word is given a choice of definitions : 1. A nervous disease ; more especially a functional disorder of the nervous system. 2. In psychiatry, a relatively minor disorder of the psychic constitution ; in contrast with the psychosis, it is less incapacitating, and in it the personality remains more or less intact. Sometimes called psychoneurosis. Thereafter, among a long list, one can read that accident neurosis is a neurosis with hysterical symptoms caused by accident or injury, and that traumatic neurosis is one which results from an injury. It would weary you to amplify, but what in fact does it all mean ? No one will deny the good faith of these important authors, only their helpfulness in this subject is disputed, since the unwary are too often betrayed by an exchange of words for knowledge. This, in effect, is the very

essence of the problem, since so much of our understanding is bemused by vague thinking which passes for learning let alone knowledge.

The effect of trauma on the mind is conditioned by conscious thought which in turn is under the influence of subconscious processes. This involves diathesis and character, together with an incalculable something that we regard as personality, all adding up in an individual to a state for which at present we have no reliable yardstick or measure. These factors are egocentric, but when an incident occurs a further consideration arises due to suggestion accruing from the circumstances of the accident ; the aggregation of all these resulting in the behaviour of the person during the weeks and months following the injury.

INTERPRETATION OF DELAYED NEUROSIS FOLLOWING ACCIDENT.—

T. B., aged 35, a shaftsman in the mine ceased work on 3rd April 1946, claiming to be unfit on account of " an injured leg and shock " which he attributes to be the result of an injury he sustained in September 1943. At that time apparently he was engaged at the installation of some new plant in the shaft and was in the act of transferring a pipe from one rope to another. The signal had been sent to the winding engineman to lower the cage but instead of doing so the cage was pulled back and the man was thrown over a beam and had to climb part of the shaft. I saw him on 25th May 1946, when in addition to these details he told me that he was not unconscious and the bruising of the leg only necessitated his remaining at home for five days. After this he did light work for six weeks and then obtained other occupation of ordinary work in the mine. Later, in about six months, he resumed his usual work but in another pit; however, at the end of February this year he went to his original post in the pit where the accident occurred. After five weeks of this he was unable to continue because of increasing weakness in his back and a feeling of nervous strain. In answer to questioning he alleges that these sensations have been present in varying degree since the accident, sufficiently on one or two occasions to keep him off work for a week or so at a time. He admitted that the original shaft haunted his thought and that, while able to continue at other work, he had a horror of his original job, and always opposed the suggestion that he return until he finally did so with, what he termed, the inevitable result. Since being idle he alleges that his symptoms have become steadily worse.

In appearance the man had a good colour and was well nourished. He moved carefully and slowly, holding himself stiffly. Hands were tremulous and reflexes lively but there were no signs of injury and no indication of organic disease in the nervous system or elsewhere, but the pulse rate was rapid at 100 per minute.

My summary of this case was : that the immediate effects of the accident in September 1943 were slight, but gradually an anxiety has developed which is said to be increasing. It is a typical functional state and not associated with any signs of organic disease. In my view the condition is not due to the accident as such but is compatible with an attitude of mind that has developed and been elaborated by a subconscious dislike of his particular place of work : aggravated by suggestion coming from friends and others. Had the workman

not returned on February last to his original location, the present state of anxiety neurosis would probably never have arisen.

That, of course is my honest view reached by normal medical processes of deduction and assessment. One is convinced of its truth in fact, but this is an instance where the processes of medicine, perhaps aided by what the cynics call a hunch, come into conflict with the logic of the law whose representative will call dramatic attention to the far reaching emotional disturbance to the man of the grim possibilities inherent in the circumstances of the original accident and the present cruelty of endeavouring to establish that the claimant was work-shy. In this case a haunting fear was the dominant factor, to the exclusion of all others, including compensation. Yet how frequently in the attitude of to-day, pandering to the popular trend, would all attention have been drawn to the financial motive.

Two people of like age may receive a similar blow, the one at football, the other at work, neither really serious, yet while one recovers spontaneously, the other frequently undergoes a lengthy period of invalidism. Surely it is something more than the presence or absence of inducement. In a sense the subconscious process is the same, desire to exploit the situation, the footballer gaining prestige by an early return to the game, the workman escaping from an unpleasant routine to enjoy leisure and perhaps sympathy. There the matter ended in the days before the vast experiment originated by the Workman's Compensation Act. Since the advent of this, however, a new factor has arisen which has proved to be a testing ground both for the credulity and good faith of mankind. Other countries than ours have been confronted with interpreting and applying similar legislation, and against the justice which it has brought to men's lives must be offset the proven fact that the millions spent annually increase steadily, and with the outlay an enormous addition to the army of men off work. The cumbersome machinery itself involves endless delays during which the workman's symptoms, originally a " traumatic neurosis," become transformed into a " condition neurosis " in the sustained effort required in a fight for compensation.

No sane thinker to-day would ever deny the injured workman his due right to have the best available treatment and at the same time reasonable provision for himself and his family, but the greatest evil arises from the principle of lump sum settlement which provides a happy hunting ground for the less scrupulous type of lawyer and even more importantly a sustained mental collision for the victim.

To distinguish between neurosis and malingering is a relatively simple clinical procedure, and yet the medical literature on the neuroses following trauma is frequently tainted by an under current and by an unwarranted hostility and antagonism toward the neurotic, implying that he too is a simulator, thus losing sight of the fundamental nature of the condition. This attitude does much harm in its perpetual denouncing of the neurotic and in the condemnation of his inevitable

desire for compensation. Whereas so often it is not the victim himself who first thinks of the matter but more frequently his friends and advisers, the injured being stampeded by these influences when he comes to recognise the amazing therapeutic indifference of the many medical men who confront him as the case develops along the usual partisan lines. Then he begins to sort out those who are for him from those who are against and conditions himself accordingly. The physician who is there to alleviate human suffering often adds insult to injury by his manner, which undoubtedly traumatises the psyche of the injured, and does much to bring about secondary elaborations.

The " wish for compensation " explanation has been so publicised to the extent that it masks the vastly more complicated etiology of the psychoneurosis. This persistent notion has tended to oversimplify the whole problem, but one has seen too many cases where the measure of secondary gain from continued illness is insufficient to account for such lasting disability.

Not infrequently one has observed a workman with a highly developed sense of family responsibility who has continued at work after injury in spite of subjective symptoms such as dizziness, back pain and headache, who makes no claim for compensation and does not show secondary elaborations. The success of such an effort depends on a number of factors—intensity of the symptoms, character of the work, make up of the individual. Proper guidance and psychotherapy in the very beginning of the illness are important. Our best approach medically is to regard compensation as, at most, offering merely a secondary gain from illness.

Some years ago as a result of a disastrous mine explosion I had the opportunity of observing very closely the gradual development of this secondary elaboration in a group of over twenty men who had experienced relatively the same type of accident. At first each case had its own individuality and personal variation of symptoms, not untempered with relief that Providence had spared a worse fate, but slowly as time dragged on, with the inevitable group discussion and example, each of these men evolved an indistinguishable neurosis pattern that was pathetic to witness. Superficially it might be regarded as the herd instinct towards reward, but as one got to know these men the complexities of each problem became increasingly apparent.

The point I should like to make is this :—that a useful experiment might have been made by persuading every second man immediately after the accident to do a job within his capacity, probably much easier than his normal work, but at a similar wage. Then the future progress of each group could have been watched with a control for comparison at every stage.

CONCLUSION.—The most conflicting opinions concerning the organic effects of trauma on the nervous system are to be found in the vast amount of available literature. I have attempted within the limits of this paper to indicate the present position of our knowledge

as I see it, hoping to avoid the aspersion of being dogmatic, since
such an attitude as yet has little to commend it. Nonetheless we
must try thoughtfully and faithfully to see what light there is, expecting
in time to build up the truth on a foundation of fact.

In the post-traumatic neurasthenias and post-traumatic hysterias,
as I feel they should be called, one has laid emphasis on the intervening
period of meditation and suggestion, while trying to relegate the
question of compensation to a more subsidiary role than is given to
it by many who are guided mainly by the fashion of the times and
enjoy a simple explanation where indeed none exists.

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THE TREATMENT OF PULMONARY TUBERCULOSIS DURING THE PAST FIFTY YEARS *

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INTRODUCTION : THE SANATORIUM.—As a preliminary to our survey of the treatment of pulmonary tuberculosis during the past fifty years, let us cast our minds back to the year 1896 and take stock of the therapeutic position as it was at that time. Much had happened during the century which was then drawing to its close and the literature on phthisis was blazoned with the names of men whose painstaking research was shedding a new light on one of the major medical mysteries of the Middle Ages. The morbid anatomists had placed the pathology of the disease on a sure foundation, Villemin had demonstrated the transferability of the tubercle from animal to animal, and Koch had shaken the medical world with his demonstration of the causative organism. In Germany, *Hermann Brehmer* had established the first sanatorium at Goerbersdorf in Silesia and his example had been quickly followed by Peter Dettweiler and by Otto Walther. In Britain, the *Brompton Hospital* had been established for some fifty-five years and here, in our own city of Edinburgh, the *Royal Victoria Dispensary* had been founded in 1887, followed a year later by the opening of the Royal Victoria Hospital. Across the Atlantic, *Edward L. Trudeau* had won his own personal battle with the disease and in 1884 had founded in the Adirondeck Mountains that sanatorium which was to prove a model for the many others which quickly followed. The idea of the sanatorium had been born, and throughout the world the inauguration of the hygienic-dietetic treatment of tuberculosis was under weigh. Other important events having a profound bearing on therapeusis were pending, and these we shall consider in due course, but for the moment let us confine our attention to the basic principles of treatment and see in what light they were regarded fifty years ago. In the year 1898 the July number of the *British Medical Journal* contained an article by *Dr Robert Philip* on " The Universal Applicability of the Open-Air Treatment of Pulmonary Tuberculosis " in which he discussed the methods of treatment then in practice at the Royal Victoria Hospital in Edinburgh. He summarised the essential features of the treatment as follows :—

(1) free access of air and sunlight into the rooms ;
(2) an out-of-door life ;

* Read at a meeting of the Tuberculosis Society of Scotland, held in Edinburgh on 10th May 1946.

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(3) graduated exercise including light dumb-bell or Indian Club exercises, golf, quoit throwing and cycling ;

(4) daily bathing ;

(5) an adequate diet with three main meals and two snacks daily.

Medicines played but little part in the scheme of treatment, the only two mentioned being cod liver oil and arsenic.

It is interesting to note the author's comments on the results of this treatment : " In so chronic and treacherous a disease it is not wise to speak confidently of cures effected. The proportion of patients, however, who have left the hospital and maintained for years continually good health and been able to resume regular work, perhaps with a change of employment, is a large one. On the other hand disappointments are frequent." Dealing with the causes of these disappointments, Dr Philip remarked, " In the first place our patients are chiefly in poor circumstances and are compelled too rapidly to resume the conditions of life which induced the disease, and secondly the resources of the institution are so limited and the demands so enormous that the patients' stay in hospital has often to be curtailed where it ought to be prolonged." Forty-eight years later we have still not succeeded in solving the problem of the waiting list.

It will be noted that the emphasis in treatment was placed on fresh air and graduated exercise rather than on rest, a regimen which was powerfully supported by *Marcus Paterson* and his imitators in subsequent years. The influence of Paterson exercised a profound effect on the treatment of pulmonary tuberculosis in Britain, and the Frimley system of exercise and controlled auto-inoculation was widely practised in British sanatoria long after its fallacies had become obvious. On the Continent and in America the enthusiasm for exercise never outstepped the bounds of discretion to the same extent as it did here, and while our patients were being encouraged to wield the axe and the pick (it is recorded that the working achievements of the Frimley patients included the excavation and concreting of a 500,000 gallon reservoir (Powell and Hartley, 1921)) others were discovering the benefits to be derived from prolonged and intensive rest. In due course the lesson was learnt and slowly the pendulum swung. The modern view was well expressed by *Willis* (1944) when he said " A scheme of much more rigorously maintained bed rest regimen has come into use. Emphasis is more and more being placed upon placidity of mind and body as essential to early recovery. The patient is being told as never before of the advantages of relaxation. He is fortunate who can lie still for long hours each day without anxiety or impatience—waiting quietly for time and " the cure " to return him to health and home." In March 1946, in the latest number of our British journal, *Tubercle*, we find a brief account of the work being carried out at one of the English sanatoria containing these words : " Treatment follows established principles, more emphasis now being

placed on rest and food, an excess of fresh air not being considered essential or even desirable. The theory of auto-inoculation has been abandoned and exercise and work, being part of the process of rehabilitation, are not pushed to extreme limits."

RADIOLOGY.—While this alteration in the fundamental principles of the treatment of the disease was taking place other and more dramatic events were crowding the stage, events which were to prove revolutionary and to make our half century a peculiarly fascinating period. Fifty years ago, *Wilhelm Conrad Röntgen* had just communicated to the world his discovery of the Röntgen ray, which was to open up new vistas in phthisiology affecting not only diagnosis but also case assessment and management. The nineteenth century expert was dependent for diagnosis upon his ear and, to a lesser extent, upon his senses of touch and sight. Now he was to see the changes in the lung shown as shadows upon the screen and the film. As Sylvanus Thompson has written, " November the 8th 1895 will ever be memorable in the history of science. On that day a light which so far as human observation goes, never was on sea or land, was first discovered." If one might digress for a moment to touch on the less scientific side of this memorable discovery it is interesting to note that within a few weeks of its announcement a firm in London was advertising the sale of X-ray-proof underclothing, and it is said (Brown 1941) that in February 1896 an attempt was made to introduce a bill into the State Legislature of New Jersey prohibiting the use of X-rays in opera glasses in theatres.

In a matter of weeks physicians were fluoroscoping the chest and watching in amazement the heartbeat and the diaphragmatic excursion, but a long period of controversy and scepticism was to ensue before the skiagram won for itself a place in the diagnosis of pulmonary tuberculosis. It is probable that the first paper on this subject was that presented by *Béclère and Mignon* before the Fourth Congress for the Study of Tuberculosis held in Paris on 29th July 1898, a year after *Rosenfeld* had published what is believed to be the first röntgeno-gram of the lung. It is unnecessary to examine in detail the struggles of those early pioneers against the criticism of their contemporaries and the imperfection of instruments and materials. The results which they achieved were little short of amazing, and I read recently a reprint of a paper in the *Lancet* of 25th July 1903 by *Lawson and Crombie* in which they described and illustrated the radiological appearance of chronic fibroid phthisis, of cavitation, of atelectasis and of emphysema with most remarkable accuracy. By 1906 the pioneer period had passed and the succeeding ten years were to see the value of radiography in the diagnosis of diseases of the chest definitely established. From 1916 to 1925 might be called the period of expansion. The sanatorium physicians were entering the X-ray field and experience in the use of the method was emphasizing more and more forcibly the limitations of physical signs. An X-ray

classification of pulmonary tuberculosis was growing up. In 1923 *Gräff and Küpferle* published their atlas " *Die Lungenphthise*," replete with fundamental knowledge for the interpretation of many of the shadows seen, and the interpretation of these shadows in terms of pathology and their prognostic significance were becoming vital issues. Fine points of differentiation were now being discussed and tuberculosis specialists were putting patients to bed on the strength of the evidence provided by the skiagram. Cavitation was being treated by collapse therapy, and the value of the screen in the control of artificial pneumothorax was being recognised. From 1925 onwards events moved rapidly, and by 1930 a sanatorium without an X-ray department had become an anachronism. No longer was it simply a method for diagnosis and for the control of collapse therapy—advancing technical improvements were making it an accurate means of assessing progress of a case whilst under treatment. By 1935 sanatoria were using a routine monthly film of the chest as a guide to progress, and the reign of the thermometer was over. In 1935, we first heard of *tomography*, originating in Germany and introduced into Britain by *MacDougall* and the late *E. W. Twining*. Their work gained rapid recognition, and to-day tomography has won its spurs and has become a routine procedure when considering candidates for major surgery or for bilateral collapse.

COLLAPSE THERAPY : PNEUMOTHORAX.—And now what of collapse therapy and the surgical treatment of pulmonary tuberculosis ? Fifty years ago the name of *Carlo Forlanini* was virtually unknown in Britain although for some years previously he had been working on his idea of producing pulmonary collapse by the introduction of intrapleural air. Until 1900, however, his publications appeared only in Italian, with the exception of a brief notice in the *Medizinische Wochenschrift* of Munich in 1894 which read : " Based on the repeated favourable influence of pleural fluid and of pneumothorax in the course of phthisis Forlanini had made a research on the living and treated two cases with favourable results. The pneumothorax can naturally be used only on one side. The pleura bears the presence of air well, any reaction or irritation or any harmful influence was not observed. Oxygen was more quickly absorbed than nitrogen which is now used to produce pneumothorax. The operation must be slowly and gradually performed, each day a small quantity of nitrogen being introduced ; if it be absorbed the quantity must be increased. The absorption capacity of the pleura lessens as time goes on. After some months the interval between injections can be lengthened." Published fifty-two years ago it is remarkable how little would require to be altered in that paragraph to-day. Although Forlanini's first successful case of artificial pneumothorax was described in 1895, there was a long and a hard road ahead before the full potentialities of this method were recognised, and it was not until the International Congress in 1912 that he received the acclamation

which was his due. Before his death in 1918, however, he had the satisfaction of knowing that his work was not in vain and that his must forever be one of the great names in the history of pulmonary tuberculosis. Many modifications have, of course, been made in Forlanini's method of using artificial pneumothorax, for he believed that to be effective a pneumothorax should have a volume and pressure sufficient to ensure continuous and uninterrupted immobilisation of the lung. This was later seen to be unnecessary, and it was soon learnt also that the high intrapleural pressures required to bring about such immobilisation were definitely harmful. It was *Ascoli*, another Italian physician, who first suggested hypotensive pneumothorax, and who later initiated the idea of simultaneous bilateral collapse, thus disproving Forlanini's principles that the tuberculous lung must be kept under total collapse and that the collapse could be applied to one side only. In America, the initial work on artificial pneumothorax was carried out by that forceful personality, *John B. Murphy* of Chicago. His technique was interesting in that he gave but one injection of air, a formidable one of at least 1200 c.c., and thereafter left the lung to its fate. In determining the quantity of air to be injected he was guided by the distress of the patient, the dyspnœa and the degree of mediastinal displacement. Murphy did but seven cases in all, as he quickly came to the conclusion that the operation was so simple that it could be safely left to the physician —a decision which, considering Murphy's somewhat daring methods, was probably one to be applauded. From Murphy and Chicago our study takes us again to Europe and to Christian Saugman of Copenhagen who, stimulated by Murphy's publication of his method, began the practice of pneumothorax in Denmark and who, in 1904, introduced the water manometer into his apparatus for routine use, thereby contributing immeasurably to the safety of the operation. The principle of and the tools for pneumothorax were now complete, and it remained for many workers to refine technique and indications and for pioneers in each country to popularise the method. It would be fascinating to trace the development of this treatment on the Continent and to review again the names of those to whose work we owe so much, but we must move on to the year 1910. In that year *Claude Lillingston* returned to Britain from Norway, where he had been undergoing sanatorium treatment and where he had had an artificial pneumothorax successfully induced. No one in Britain was practising this treatment as yet and so his first refill was administered by himself—with the assistance of his wife. His second was given by *Vere Pearson* at Mundesley Sanatorium (Pearson, 1942) and shortly afterwards Lillingston himself carried out the first British induction of a pneumothorax at Mundesley. The names of Lillingston and Pearson are preserved for us in the apparatus which they devised, the first model of which was constructed under their supervision by the sanatorium gardener. There was the usual protracted incubation period while

the new method was critically scrutinised, and for some years its application remained in the hands of a select few. *Parry Morgan* was the first physician in this country to suggest and practise selective pneumothorax, and in 1920 *Fernandez* recorded six cases treated by simultaneous bilateral collapse, but in spite of this evidence of thoughtful and enterprising work progress was slow, and we find *Carling* (1920) recording results in 54 cases prefaced by these words : " This treatment has only been attempted in cases that were doing no good on ordinary lines and for whom, therefore, the outlook was thoroughly bad : all have been either advanced or acute, and all presented more or less unilateral disease." Small wonder that the results of these 54 cases were unimpressive or that the author felt constrained to remark in the concluding paragraph that " the treatment requires some facing and patients are much more helped by seeing good results in the flesh than by any explanation of the theory." Notable work by *Clive Rivière* and by *L. S. T. Burrell* did much to put pneumothorax on the therapeutic map ; the indications for its employment were gradually widened and as the nineteen-twenties rolled on it came to be regarded as the treatment of choice for pulmonary tuberculosis. While many spectacular results have been rightly claimed for pneumothorax there have also been many failures, and it has taken time and experience to demonstrate its limitations. The contemplation of tuberculous empyemata, broncho-pleural fistulæ and unexpandable lungs have had a salutary effect in curbing over-enthusiasm and in teaching us that an ill-considered pneumothorax can have a nasty sting in its tail, however gratifying the immediate result may have been. The past ten years have seen the rationalisation of the treatment, and the recent pertinent observations of Rafferty (1944) have summarised admirably the present position. We know that in many cases the complications of pneumothorax can be avoided by a more judicious selection of cases and that pneumothorax is not invariably the first step in any programme of collapse therapy. We have learnt that acute pneumonic disease, the thick-walled apical cavity and the presence of tracheo-bronchial disease are definite contraindications and, perhaps most important of all, we have at last grasped the imperative necessity for terminating a contra-selective collapse at an early stage.

Before leaving the subject of pneumothorax let us glance backwards to the year 1913 when, in Stockholm, *Hans Christian Jacobaeus* was striving to overcome one of the major obstacles to the success of the treatment. Pleural adhesions had prevented effective collapse in many cases, and it was in 1915 that Jacobaeus first described his instrument and his technique for closed intrapleural pneumolysis to replace the much more dangerous procedure of open division of adhesions introduced in 1908 by Friedrich. The usual latent period ensued, but the successful results which were achieved by Jacobaeus could not be denied, and the popularity of the operation steadily

increased throughout the nineteen-twenties. Its scope was widened still further in 1924 when Eloesser and Brown proposed to enucleate the parietal ends of short adhesions from the thoracic wall. In Britain the late *F. G. Chandler* and *Peter Edwards* were early in the field and did much to establish the operation as an essential part of pneumothorax therapy. It has added greatly to the effectiveness of pneumothorax, and to-day almost every sanatorium in the country is or should be in a position to have adhesion section carried out in its own neighbourhood. In experienced hands it is relatively safe but, like many other operations in tuberculosis work, it is perhaps not quite so simple as it looks, and for the inexperienced and the over-enthusiastic the potentialities for disaster are considerable.

THORACOPLASTIC OPERATIONS.—Thus far in our review we have been concerned mainly with the part played by the physician in this half-century's assault on the disease, but during that time the surgeons had not been idle, and in their own robust way had been chopping and carving at the thoracic wall since 1885, when *de Cerenville* conceived the idea of relaxing a tuberculous lung by operating on the overlying bony cage. In 1896, *Turban*, working along the lines suggested by de Cerenville and Spengler, was operating on an extensive and progressive unilateral lesion and by resection of portions of ribs 4 to 9 secured an excellent result. The next stage in the development of thoracoplasty came from *Brauer*, who was the first to realise that clinical success depended upon the production of a pulmonary collapse comparable in amount with that obtained by induced pneumothorax. In conjunction with *Friedrich* he devised the operation of total thoracoplasty, and in this case " total " was the operative word. With true German thoroughness they removed the whole bony framework of one half of the chest. The first operation of this type was conducted by Friedrich on 11th December 1907 and the patient, a certain Monsieur Cordier, survived the performance and 'fourteen months later his condition was greatly improved. All honour to Monsieur Cordier ! Unfortunately the patients who followed him were cast in less heroic mould and failed to survive the shock, the mediastinal flutter and the respiratory embarrassment which inevitably accompanied such very drastic surgery. A less dangerous alternative was obviously necessary, and *Wilms* (1914) and *Sauerbruch* (1913), working independently, evolved the paravertebral thoracoplasty in which limited portions of rib were resected posteriorily. It was this operation which was the immediate precursor of our present-day thoracoplasty and which was practised in many Continental centres and later in Britain until ten years ago. The results, however, were never completely satisfactory owing to the problem of the thick-walled apical cavity. Many such cavities, while reduced in size by the rib resection, remained as residual slits suspended from the thoracic dome, and thus the operation failed in its main objective of cavity closure. This difficulty was finally resolved in 1935 by the work of *Carl Semb*

of Oslo, who devised the modern thoracoplasty which consists of rib resection combined with extrafascial apicolysis, thus securing vertical as well as lateral relaxation. Semb's technique was brilliantly successful and in 1942 *Price Thomas* was able to demonstrate that its introduction had doubled the number of favourable results achieved by lateral thoracoplasty alone.

PHRENIC INTERRUPTION.—Minor surgical procedures of infinite variety and ingenuity have been suggested and tried from time to time, but few of them have found a permanent place in the scheme of treatment. *Stuertz*, in 1911, proposed unilateral diaphragmatic paralysis to relax a diseased lower lobe in which pleural adhesions prevented the induction of a pneumothorax, and in 1913 Sauerbruch reported favourable results following this operation in three cases. Originally the paralysis was obtained by simple section of the main phrenic nerve trunk, but in 1922 *Felix* suggested evulsion of the nerve in order to deal with any existing accessory branches which might join the main nerve deep in the thorax. For many years phrenic evulsion remained the standard operation in spite of misgivings voiced from time to time as to the wisdom of permanent abolition of diaphragmatic function. Phrenic paralysis enjoyed a tremendous popularity between the years 1927 and 1935. It appealed alike to physician, surgeon and patient as being a concrete bit of action, a surgical operation, and, best of all, apparently devoid of risk. The literature of those years bears testimony to the enthusiasm with which the phrenic nerve was attacked, for example, *O'Brien's* publication in 1930 of his results in 500 cases. From 1935 onwards, however, a more conservative attitude prevailed ; the failure of a pneumothorax was not automatically the signal for the performance of diaphragmatic paralysis, and the temporary operation, in which the nerve was crushed, rapidly replaced the evulsion. Temporary phrenic paralysis remains the most valuable minor surgical procedure to-day, providing that it is used with discrimination and not asked to achieve the impossible. It is no use sending a boy to do a horse's job, and relaxation of the diaphragm will not close a thick-walled apical cavity.

The value of phrenic paralysis has been greatly enhanced by the use of artificial pneumoperitoneum, a procedure first reported by Vadja in 1933 and subsequently elaborated by Banyai (1934) and by Joannides and Schlack (1936). Increasing experience in the use of this method is confirming the claims made for it by its originators, and personal experience of some 50 cases has convinced me of its value.

PULMONARY RESECTION.—The possibility of pulmonary resection has been mooted from time to time as, of course, the idea of actual removal of the portion of lung containing tuberculous lesions is an attractive one. *Tuffier*, in 1891, recorded a successful case where an indurated tuberculous area in an upper lobe was removed through the second intercostal space, and various other sporadic attempts at

removal were made during the next forty years, including *Maccwen's* famous case in 1906. Recently there has been an acute outbreak of resection in the United States, of which the 61 cases of *Overholt and Wilson* (1945) and the 32 cases of *Janes* (1945) are the most striking manifestations. Their results, however, are early results only, and we are yet in no position to assess the long term possibilities of lobectomy and pneumonectomy for pulmonary tuberculosis or to lay down definite indications for the operations. It is possible that, in certain cases presenting either cavernous lesions with severe bronchial stenosis, basal cavities which have failed to respond to pneumothorax and phrenic paralysis, or residual cavities persisting after a modern thoracoplasty, resection may eventually prove to be the treatment of choice, but further than this I do not think that it is possible to go on the available evidence.

OTHER SURGICAL MEASURES.—Operative ingenuity has not, of course, ended with the procedures which have been mentioned so far. Other comets have flashed across the surgical sky during these fifty years to fade as quickly as they came. Scalenectomy, multiple intercostal nerve paralysis and induced bronchial stenosis, to name but a few, are now no longer mentioned. Extrapleural pneumolysis with its filling, first of paraffin and later of air, lingered on for some years, but has now been virtually abandoned, while the same applies to the transpleural drainage of cavities introduced so hopefully by *Monaldi* in 1935. In the obstetrical history of thoracic surgery, however, the miscarriages have been few and we have ample compensation in those lusty offspring which have now come to full maturity.

ANTIGENIC AND CHEMO-THERAPEUTIC AGENTS.—Turning back once more to more purely medical problems, the search for the magic potion which will eliminate the tubercle bacillus from the body has been pursued relentlessly throughout the years, and equally relentlessly success has eluded the pursuers. Tuberculin faded from the scene years ago, at least as far as pulmonary tuberculosis is concerned, and gold salts are now steadily declining in popularity. Cadmium has also been tried and found wanting, and calcium once popular, is now little more than a placebo.

The intensive chemotherapeutic research of the past ten years has been extended to tuberculosis; and promin, diasone and promizole have followed each other in rapid succession. There is nothing to suggest that any of these substances is the answer to our problem and we must await further reports on streptomycin, the latest product under trial (Feldman, Hinshaw and Mann 1945). So far streptomycin has shown most striking bacteriostatic and bactericidal action *in vitro* and in experimental animals, but the crucial test of its application to human tuberculosis has yet to come. Whether the discovery of the effective chemotherapeutic agent for tuberculosis in man will come in the near or in the remote future one cannot foretell, but I believe that it will come and that in our time we shall reach the

rainbow's end and lay hands upon that crock of gold for which physicians have sought throughout the centuries.

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NOTES

A QUARTERLY meeting of the College was held on 5th November, the President,
Dr D. M. Lyon, in the Chair.

Royal College of Physicians of Edinburgh
Dr Alexander MacAndrew Gillespie, O.B.E. (Edinburgh), Dr Alistair Mitchell MacDonald (Edinburgh), Dr Robert Alexander Miller (Edinburgh), Dr Gordon Oliver Horne (Edinburgh), Dr Robert James Kellar, M.B.E. (Edinburgh), Dr Gordon Douglas Malcolm (Bridge of Earn, Perthshire) and Sir Andrew Davidson (Edinburgh) were introduced and took their seats as Fellows of the College.

Dr Henry James Parish (Petts Wood, Kent), Dr Percival Vivian Pritchard (London), Dr Robert Carmichael Wood (Edinburgh), Dr Pramatha Nath Bardhan (Ferozepore, Punjab), Dr Hugh Michael Denne Shepherd (Shanklin, I.o.W.), Dr John Alexander Malloch (Edinburgh), Dr John William Durell Goodall (I.M.S.), Dr John Mackay-Dick (R.A.M.C.) and Dr David Murdoch Anderson (Braintree, Essex) were elected Fellows of the College.

Drs Albert Rabinowitz (Johannesburg, S.A.), Andries Brink (Germiston, S.A.), Walter Henderson (Edinburgh), John Harold Derek Millar, M.B.E. (Edinburgh), Roderick Henry Mackay Ross (Darlington), Lala Surajnandan Prasad (Bihar, India), Neil Simson Gordon (Edinburgh), George Henderson Armitage (Cumnock, Ayrshire), Martin Matthew Whittet (Glasgow), Elizabeth Marion Hislop (Edinburgh), and Ian Wang (Edinburgh) were elected Members of the College.

The Cullen Prize, 1946, was awarded to Lt.-Col. W. F. Harvey, C.I.E.

The Hill Pattison-Struthers Bursaries in Anatomy and Physiology were awarded to Mr Morris Cyril Berenbaum and Mr James Jackson.

The Hill Pattison-Struthers Bursary in Clinical Medicine was awarded to Dr John Lamptey Quartey-Vanderpuije.

AT the annual meeting of the College, held on 16th October 1946, the
following Office-Bearers were elected for the ensuing
Royal College of Surgeons of Edinburgh
year: — *President*, Mr James M. Graham; *Vice-President*, Professor Robert William Johnstone, C.B.E.; *Secretary and Treasurer*, Mr K. Paterson Brown; *President's Council*, Professor Sir John Fraser, BART., Dr G. Ewart Martin, Mr Francis E. Jardine, Mr W. Quarry Wood, Mr Walter Mercer, Professor J. R. Learmonth, C.B.E. *Representative on the General Medical Council*, Sir Henry Wade, C.M.G., D.S.O. *Convener of Museum Committee*, Mr W. Quarry Wood. *Librarian*, Dr Douglas Guthrie.

At a meeting of the Royal College of Surgeons of Edinburgh, held on 16th October 1946, Mr James M. Graham, President, in the Chair, the following who passed the requisite examinations were admitted Fellows: Nicholas Alders, M.D. UNIV. VIENNA 1928, M.R.C.S. ENG., L.R.C.P. LOND. 1941; Charles James Barton Anderson, M.B., CH.B. UNIV. ABERDEEN 1940; Walter Gordon Birks, M.B., B.S. UNIV. ADELAIDE 1937; Selwyn Kerry Burcher, M.B., CH.B. UNIV. OTAGO 1941; Alexander Grant Squair Calder, M.B., CH.B. UNIV. EDIN. 1937; Edward Andrews Chisholm, M.B., CH.B. UNIV. GLASG. 1943; Lionel Mace David, M.B., B.CH. UNIV. WITWATERSRAND 1935; Frederick William Thomas Davies, M.R.C.S. ENG., L.R.C.P. LOND. 1939; Arthur James Freese, M.R.C.S. ENG., L.R.C.P. LOND. 1939; Godfrey Livingstone Gale, M.B., CH.B. UNIV. BIRM. 1935; Mohandas Purushottamdas Goradia, M.B., B.S. UNIV. BOMB. 1940; James Bisdee Malcolm Green, M.R.C.S. ENG., L.R.C.P. LOND.

1936; Frederick Maurice Hanna, M.B., B.CH. TRINITY COLLEGE, DUBLIN 1934; Edward Leighton John, M.B., B.S. UNIV. LOND. 1943; Walter Gifford Kerr, M.B., CH.B. UNIV. EDIN. 1937; James Ellsworth Laing, M.B., CH.B. UNIV. EDIN. 1942; Wilhelm Hendrik Stephanus Liebenberg, MED. DOCT. ARTS UNIV. AMSTERDAM 1934; Tobias Levitt, M.R.C.S. ENG., L.R.C.P. LOND. 1934; Alastair Arthur MacGibbon, M.B., CH.B. UNIV. EDIN. 1937; James Miller McInroy, M.B., CH.B. UNIV. ST ANDREWS 1940; Thomas Barry McMurray, M.B., CH.B. UNIV. L'POOL 1941; John Mackenzie Matheson, M.B., CH.B. UNIV. EDIN. 1936; Kripa Nanda Mitra, M.B., B.S. UNIV. PATNA 1939; Robert Francis O'Driscoll, M.B., B.CH. NAT. UNIV. IREL. 1940; Geoffrey Vaughan Osborne, M.B., CH.B. UNIV. L'POOL 1940; Anthony Phillip Rozario Pinto, M.B., B.S. UNIV. BOMB. 1940; Elton Carlyle Richardson, L.R.C.P. AND S. EDIN. (TRIPLE) 1941; George Keith Riddoch, M.B., B.CH. UNIV. CAMB. 1941; Leslie John Roy, M.B., CH.B. UNIV. OTAGO 1936; Alexander Robertson Taylor, M.B., CH.B. UNIV. ABERDEEN 1941; David James Waterston, M.B., CH.B. UNIV. EDIN. 1933; Austen Young, M.B., CH.B. UNIV. EDIN. 1937.

THE examinations of the Board of the Royal College of Physicians of Edinburgh, the Royal College of Surgeons of Edinburgh, and
Triple Qualification Board
the Royal Faculty of Physicians and Surgeons of Glasgow have just concluded at Edinburgh. The following passed the Final Examinations, and were granted the diploma of L.R.C.P. EDIN., L.R.C.S. EDIN., L.R.F.P. AND S. GLASG. :—Flora Sophia Barry, Athelstan Blench, Charles Kenneth Brown, Philip Arthur Clarke, Eric Dalgleish Cloughley, Thomas Corrie, Hilda Myfanwy Davies, Harry Fernbach, John Hamilton, Phaik-Lin Lim, Peter Alexander Ronald Lornie, Anna Majzlisz, Frederick Richard Moreland, John McLaughlin, John Ashton Pool, Edwin Wilson Russell, Richard Short, Edward Silverstone, Hector John Stott, Paul John Vertannes, David Tinsley Wilson, Julius Zucker.

AT a Graduation Ceremonial held in the Upper Library on Saturday, 26th October 1946, the following diplomas were
University of Edinburgh
conferred :—
Faculty of Medicine—Diploma in Public Health:—
Lewis Sutherland Anderson, B.SC., M.B., CH.B. (MANCHESTER); Harry Acroyd Barker, M.B., CH.B.; Alexander David Christian Stewart Cameron, M.B., CH.B.; Edward Campbell, M.B., CH.B.; King Ho Cheung, M.B., B.S. (Hong Kong); Pat Spence Clouston, M.B., CH.B.; James Russell Gray, M.B., CH.B.; William Woodman Hutton, M.A., M.B., CH.B.; Robert Sinclair Kennedy, M.B., CH.B. (ST ANDREWS); Ralph Israel Sindell Lewis, M.B., CH.B.; David Alexander Lowe, M.B., CH.B.; Donald Ian M'Callum, M.B., CH.B.; David M'Gowan, M.B., CH.B. (GLASG.); Isobel Patricia MacKenzie, M.B., CH.B.; John Magnus Mair, M.B., CH.B. (ABERDEEN); Wilfrid Graham Pollard, M.B., CH.B.; Kenneth David Glover Reid, M.B., CH.B.; Douglas Stuart Ferguson Robertson, M.B., CH.B.; Richard Scott, M.D.; John Emerson, Simpson, M.R.C.S. (ENG.), L.R.C.P. (LONDON); John Sleigh, M.B., CH.B. (ABERDEEN); Bernard Snell, L.R.C.P. (ED.), L.R.C.S. (ED.), L.R.F.P. AND S. (GLASG.); Daniel Thomson, M.B., CH.B. (ST AND.).
*Diploma in Medical Radiology:—*Peter Aitken, M.B., CH.B.; Margaret Dickson Cameron, M.B., CH.B. (ABERDEEN); Norman Saks, M.B., CH.B. (WITWATERSRAND); Alexander Colin Peter Duguid Thomson, M.B., CH.B.; John Calder Wood, M.B., CH.B. (GLASGOW).

NEW BOOK

Morell Mackenzie: the Story of a Victorian Tragedy. By R. SCOTT STEVENSON.
Pp. 190. London: Wm. Heinemann. 1946. Price 15s.

Sir Morell Mackenzie, who died in 1892 at the age of fifty-four, was one of the pioneers of British laryngology and the author of a text-book which still retains its value as a work of reference. It is unfortunate that he is remembered chiefly on account of his association with the tragic case of the German Crown Prince Frederick, father of the notorious Kaiser William. Mackenzie was at the summit of his career in London when he was called to this distinguished patient on 18th May 1887. On arrival at Berlin he found the German surgeons in attendance prepared to operate upon what they regarded as a case of cancer of the larynx. The final decision had been left to Mackenzie, who now counselled delay as he was satisfied neither with the diagnosis nor with the prospects of operative treatment. In Mr Scott Stevenson's view, "the stand Mackenzie took regarding the operation was perfectly correct and entirely justified." The majority of surgeons at that time regarded complete excision of the larynx with disfavour, and even the partial operation of laryngo-fissure was associated with a high mortality and scant success. A piece of tissue, removed by Mackenzie, was submitted to Professor Virchow, whose report was inconclusive. But, as the author remarks in his final chapter, "the whole course of the disease was far from typical and on careful examination of the available evidence there is more than a suspicion that the cancer supervened upon syphilis." So the doctors differed. The feeling against Mackenzie was strong. Meantime the disease progressed. In June, however, the patient was able to take part in the Jubilee Celebrations of his mother-in-law, Queen Victoria, and he remained in this country, under the care of Morell Mackenzie, until September. It was then decided that he should spend the winter in the mild climate of San Remo. While he was there, the diagnosis of cancer of the larynx became more and more obvious, and a palliative tracheotomy was performed in January. In March the aged Emperor died, and the mortally-ill Crown Prince hastened to Berlin to take his place as Emperor Frederick III. His reign was a short one, lasting only ninety-nine days. The liberal regime of the new ruler, which might well have inaugurated a long epoch of peace, was rudely broken by his death, and then commenced the disastrous series of events so familiar to everyone. Frederick III died on 15th June 1888, with Mackenzie in attendance. And now there burst upon the hapless laryngologist a storm which had long been brewing. The case had become by this time a subject of discussion, not only in consulting rooms, but in all the salons and drawing-rooms and clubs of Europe. Morell Mackenzie felt obliged to defend himself and, in doing so, committed his gravest error. He published a book entitled *Frederick the Noble* in which he not only gave full details of the illness but also decried, in unrestrained terms, the actions of his German colleagues. It was a foolish move which merely added fuel to the fires of controversy. Today, at a distance of half a century, it is interesting to recall the case, described and discussed in clear detail by an author who is himself both laryngologist and politician. The story is complicated and can scarcely be related without a certain degree of bias, yet Mr Scott Stevenson weaves the tale with due restraint, although it is obvious that he regards Mackenzie as one who was misunderstood, though arrogant, vain, and tactless. Incidentally, the author gives a vivid picture of the medical practice and of the political background of the Victorian Age. None can deny that the illness and death of Frederick III altered the course of history. As one follows the details of the tragedy, one cannot but admire the courage and fortitude of the distinguished patient. Morell Mackenzie also enlists our sympathy. He lost position and prestige, an individual loss which, however, was as nothing, compared to the national loss suffered by the German nation. When Frederick III died, Germany lost a great liberal leader, and acquired in his place an Emperor who precipitated a world war.

This well-written work on an absorbing theme will appeal not only to the medical profession, but to the ever widening circle of readers of history. There is a useful index and a full bibliography.

BOOKS RECEIVED

ALBRECHT, F. KENNETH, M.D.   Modern Management in Clinical Medicine.
(Baillière, Tindall & Cox, London)   55s. net.

ALLEN, EDGAR V., B.S., M.A., M.D., M.S., F.A.C.P., NELSON W. BARKER, B.A., M.D., M.S., F.A.C.P., and EDGAR A. HINES, Jr., M.D., B.S., M.A., M.S., F.A.C.P.   Peripheral Vascular Disease.
(W. B. Saunders Company, London)   50s. net.

ANDERSON, C. G., PH.D., DIP. BACT.   An Introduction to Bacteriological Chemistry.   Second Edition   *(E. & S. Livingstone Ltd., Edinburgh)*   20s. net.

AREY, LESLIE BRAINERD, PH.D., SC.D., LL.D.   Developmental Anatomy. Fifth Edition   .   .   .   *(W. B. Saunders Company, London)*   35s. net.

BERTWISTLE, A. P., M.B., CH.B., F.R.C.S.ED.   A Descriptive Atlas of Radiographs.   Sixth Edition   .   .   *(Henry Kimpton, London)*   45s. net.

COX, LEONARD B., M.D., M.R.C.P., F.R.A.C.P., and JEAN C. TOLHURST, M.SC. Human Torulosis.
((Melbourne University Press), Oxford University Press, London)   25s. net.

DAVIDOFF, LEO M., M.D., and CORNELIUS G. DYKE, M.D.   The Normal Encephalogram.   Second Edition   .   .   *(Henry Kimpton, London)*   27s. 6d. net.

DILLING, WALTER J., M.B., CH.B., M.P.S., and SAMUEL HALLAM, L.D.S., R.C.S. Dental Materia Medica, Pharmacology and Therapeutics.   Third Edition, Revised   .   .   .   .   .   *(Cassell & Co. Ltd., London)*   13s. 6d. net.

ERWIN, G. S., M.D.   Tuberculosis and Chest Disease for Nurses.
(J. & A. Churchill Ltd., London)   10s. 6d. net.

Compiled by FULTON, JOHN F., M.D., and MADELINE E. STANTON, A.B.   The Centennial of Surgical Anesthesia   .   *(Henry Schuman, New York)* $4.00

HANDFIELD-JONES, R. M., M.C., M.S., F.R.C.S.   Surgery of the Hand.   Second Edition   .   .   .   .   *(E. & S. Livingstone Ltd., Edinburgh)*   20s. net.

HUTCHINSON, HERBERT.   Jonathan Hutchinson : Life and Letters.
(Wm. Heinemann (Medical Books) Ltd., London)   12s. 6d. net.

Edited by JOHNSTON, T. B., C.B.E., M.D., and J. WHILLIS, M.D., M.S.   Gray's Anatomy : Descriptive and Applied.   Twenty-ninth Edition.
(Longmans, Green & Co., London)   70s. net.

JONES, F. WOOD, D.SC., M.SC., M.B., B.S., F.R.S., F.R.C.S.   Buchanan's Manual of Anatomy.   Seventh Edition   .   *(Baillière, Tindall & Cox, London)*   45s. net.

KIRK, ESBEN, M.D.   Acidosis   . *(Einar Munksgaard, Copenhagen, Denmark)* Dan. cr. 18.0.

McGREGOR, ALEXANDER LEE, M.CH., F.R.C.S.   A Synopsis of Surgical Anatomy.   Sixth Edition   .   .   *(John Wright & Sons Ltd., Bristol)*   25s. net.

MACINTOSH, R. R., M.A., M.D., F.R.C.S., D.A., and WILLIAM W. MUSHIN, M.A., M.B., B.S., D.A.   Physics for the Anaesthetist.
(Blackwell Scientific Publications Ltd., Oxford)   30s.

Edited by MASON, Lt.-Col. ROBERT L., M.C., A.U.S., and HAROLD A. ZINTEL, M.D.   Pre-operative and Post-operative Treatment.
(W. B. Saunders Co. Ltd., London)   35s. net.

MORRIS, HUGH, M.D., D.M.R.E.   Medical Electricity for Massage Students. Third Edition   .   .   .   .   *(J. & A. Churchill Ltd., London)*   21s. net.

MORTON, W. T. G.   Memoir on Sulphuric Ether.
(Henry Schuman, New York) $1.50

Edited by NICHOLLS, LUCIUS, C.M.G., M.D., B.C., B.A.   Aids to Tropical Hygiene.   Third Edition   .   .   *(Baillière, Tindall & Cox, London)*   6s. net.

PARRY-PRICE, HÖEL, M.R.C.S., L.R.C.P., D.A.(R.C.S.).   A Short Handbook of Practical Anaesthetics   .   .   *(John Wright & Sons Ltd., Bristol)*   12s. 6d. net.

PEEL, J. H., M.A., B.M., B.CH., F.R.C.S., F.R.C.O.G.   Textbook of Gynaecology. Second Edition .   *(William Heinemann (Medical Books) Ltd., London)*   21s. net.

SCOTT-WILSON, H. W., B.SC., B.M., B.CH.   Aids to Bacteriology.   Seventh Edition   .   .   .   .   *(Baillière, Tindall & Cox, London)*   6s. net.

SHELDON, WILFRID, M.D., F.R.C.P.   Diseases of Infancy and Childhood. Fifth Edition   .   .   .   .   *(J. & A. Churchill Ltd., London)*   —

STONE, MOSES J., M.D., and PAUL DUFAULT, M.D., F.A.C.P.   The Diagnosis and Treatment of Pulmonary Tuberculosis   .   *(Henry Kimpton, London)*   17s. 6d. net.

WEINBREN, M., B.SC., M.R.C.S., L.R.C.P., F.F.R., D.M.R.E.   A Manual of Tomography   .   .   .   .   *(H. K. Lewis & Co. Ltd., London)*   45s. net.

WRIGHT, W. D., A.R.C.S., D.SC., and L. C. MARTIN, D.SC., A.R.C.S., D.I.C. Researches on Normal and Defective Colour Vision.
(Henry Kimpton, London)   36s. net.

YELLOWLEES, HENRY, O.B.E., M.D., F.R.F.P.S., F.R.C.P., D.P.M.   The Human Approach .   .   .   .   .   *(J. & A. Churchill Ltd., London)*   10s. 6d. net.

MOLLUSCUM CONTAGIOSUM *

By R. CRANSTON LOW, M.D., F.R.C.P.E., F.R.S.E.
Consulting Physician to the Skin Department,
Royal Infirmary, Edinburgh

(*From the Department of Bacteriology, Edinburgh University*)

MOST medical men are familiar with the appearance of the lesion of molluscum contagiosum. It is a raised solid hemispherical projection of the same colour as, or slightly redder than, the normal skin. The centre of each lesion usually shows a small depression, but sometimes is capped by a rough horny-looking crust. The lesion feels solid and firm. It begins as a minute pin-point elevation and grows slowly till it reaches the size of a large pea. Whilst usually sessile, it is occasionally somewhat pedunculated. If squeezed gently with a pair of forceps, a thick whitish material like cream cheese can be expressed, and if this is placed in Liq. potassæ and examined unstained, even under the low power, but better still under the high power, one has no difficulty in recognising roundish or oval bodies—the so-called molluscum bodies— lying among the epithelial scales.

Molluscum contagiosum may occur on any area of the skin except the palms and soles. The commonest situations are the face (especially the eyelids), neck, and genital area. The number of lesions varies from one or two up to dozens, and lesions can be seen at all stages of development in the same patient. The eruption may begin as a single lesion which is followed by others in the immediate neighbourhood, or several lesions may appear more or less simultaneously on different parts of the skin. Usually there are no symptoms, but sometimes there is slight itchiness, and if the patient scratches, fresh lesions may develop along the scratch marks. Occasionally the lesion becomes infected, showing all degrees of inflammation from slight swelling and redness to suppuration. When this occurs the nearest lymphatic glands are enlarged. Lesions are said to occur sometimes on the lips and inside the mouth, but I have never seen any in these situations.

The lesions I have described are those usually seen, but molluscum contagiosum may occur in less common forms. Occasionally one sees very large giant forms either as a single large maybe pedunculated lesion or a large projecting mass with numerous umbilications on it.

* A Honyman Gillespie Lecture delivered in the Royal Infirmary.

These have occasionally been mistaken for squameous-celled carcinomas. Sometimes also the lesions of ordinary size may occur in large flat plaques of closely-set elements, and if infected and covered with crusts may simulate a crusted or warty dermatitis. A correct diagnosis can usually be made by close inspection of the lesions at the edges of the patch. Another not uncommon form of the disease is the very small, rather flat, rough umbilicated lesion which one usually sees on the hands. It looks not unlike an ordinary wart and is commonly seen on the fingers. Often no cheesy material can be expressed, and in order to make the diagnosis the centre of the lesion must be picked out with a blunt needle and examined for molluscum bodies.

As the name indicates, molluscum contagiosum has been recognised from the first as a contagious condition. If the cheesy material expressed from a lesion is rubbed on the skin of the same or another individual the disease can be readily transmitted.

The incubation period is anything from one to six months, but on the average from two to three months. It is not uncommon to see the original primary lesion surrounded by a crop of smaller, more recent ones.

The lesions increase slowly in size and may persist indefinitely for weeks or months. If left alone, some of them may shrink and gradually disappear, but the natural method of cure is usually by secondary infection taking place. The central opening of the lesion is naturally liable to infection with surface organisms. Staphylococcus, streptococcus, pneumococcus and Bacillus coli are the common infecting organisms. Non-pathogenic fungi have also been found occasionally. If near the genitals, Borrelia refringens may also be present. When infection occurs the lesion swells, and it and the surrounding skin become very red and inflamed. The nearest lymphatic glands also swell and may be tender. This inflammation may subside and the lesion gradually shrink, but usually suppuration takes place with the formation of an abscess which bursts to the surface, thus curing the lesion.

There seems to be no reason why molluscum contagiosum lesions, if not infected, should not persist indefinitely, but one finds in practice that patients usually come for treatment soon after noticing the condition. Treatment and cure of one or two lesions does not lead to spontaneous cure of the other lesions as may occur when treating the common wart. Each lesion has to be treated separately till all are cured.

Infection is spread by direct contact from person to person; for example, a nursing mother may become infected on the breast if the child has lesions on the face. It may spread in a house to several members of a family either by direct contact or probably by means of towels.

The chief source of infection, however, is the public baths, especially swimming and Turkish baths. Jonathan Hutchinson in London was the first to point out that Turkish baths were a common source of the

infection. Practically all the cases which one sees in Edinburgh are in persons who attend the fresh-water swimming-baths. Some years ago there was a small epidemic of 8 cases in boys who frequented the Warrender Park Baths in Edinburgh. The lesions were all either on the fronts of the elbows or backs of the knees. This pointed to the horizontal bar used for gymnastics being the source of the infection. After the bar was disinfected with lysol no further cases occurred. The contagion, however, is probably more commonly spread by the water or towels than by gymnastic apparatus.

Another less common method of spread is by persons with very minute lesions on the hands, especially the fingers. As they look like warts no attention is paid to them. That such lesions may be a source of spread was shown some years ago (1909) when a London surgeon (Paton) published a report that in one year seven of his operation wounds developed on the site of or near the scar typical lesions of molluscum contagiosum. As the lesions occurred in cases operated on for different diseases in different hospitals or nursing homes, the assumption was that the surgeon was to blame himself. On careful examination he discovered that two fingers of his right hand showed minute umbilicated molluscum contagiosum lesions, and from these the wounds had become infected in spite of the fact that his hands were scrubbed before the operations with soap and water and then soaked in biniodide of mercury solution.

There are also records where the infection was transmitted by tattooing and by wrestling.

Molluscum contagiosum occurs much more commonly in children and adolescents than in adults, and in Edinburgh, at least, it is more commonly seen in hospital than in private practice. It is also commoner in females than males. Numerous epidemics have been reported from time to time, chiefly in Europe and the U.S.A. Most of these occurred in schools and institutions for children. The largest epidemic recorded was 59 cases out of 350 children. In Edinburgh there has, so far as I know, been no large epidemic, but cases often appear at the hospital in small groups of 3 or 4 at a time.

I have obtained the figures for the number of cases of molluscum contagiosum seen at the Skin Department of the Royal Infirmary of Edinburgh during the last ten years. Before the war (1934-39) the number of cases averaged 78 *per annum* out of an average of 39,000 skin cases; that is 2 *per* 1000 skin cases. During the war years (1940-1944) the number of cases dropped to about half, averaging only 35 *per annum* out of an average of 25,000 skin cases, *i.e.* 1·4 *per* 1000 skin cases. This fall in the number of cases of molluscum contagiosum and in the total number of skin cases is probably due to the evacuation of so many mothers and children from the city.

In 1910 Graham Little published statistics of molluscum contagiosum for Great Britain and Ireland as follows: London, 2·1 per 1000 cases of skin disease; Newcastle, 1·0 per 1000; Manchester, 0·8 per 1000; Bristol, 0·7 per 1000; Glasgow, 0·6 per 1000; Dublin,

3·3 per 1000 ; and in 1912 the statistics of the American Dermatological Association give the figure of 1·6 per 1000 for the whole of the U.S.A.

Graham Little also records that the disease occurs fairly regularly in London, Manchester, Newcastle, Liverpool, Birmingham, Portsmouth, Bristol, Dublin, Belfast, Edinburgh, Glasgow and Aberdeen. Dr Christie of Aberdeen found it mostly on the arms of girls working in the fish market. On the other hand the disease was practically unknown in Leeds, Sheffield, Nottingham, Hull, Lincoln, Shrewsbury, Oxford and Cambridge. Graham Little points out the interesting fact that with the exception of Manchester and Birmingham all the places where it has been reported at all frequently are sea-ports, whilst with the exception of Hull all the places where it is practically unknown are inland. What interpretation to place on these facts is not very clear, and as so many factors are involved one might speculate indefinitely as to whether they have any significance or not.

Besides being well known in this country and the U.S.A., molluscum contagiosum has been reported all over Europe, many parts of Africa, South America and Asia, so that its distribution is world-wide.

The disease was first described by Bateman of London in 1817. In his *Atlas and Practical Synopsis of Cutaneous Diseases* he shows two plates under the heading of molluscum. In one he figures numerous rounded and oval nodules in the skin, many of them pedunculated and pendulous, scattered over the body and limbs of an adult. These had grown slowly, continued through life without symptoms and were undoubtedly molluscum fibrosum. In the other plate he figures typical small and large lesions of molluscum contagiosum, some of them suppurating, on the face and neck of a young woman. He states that this woman had been infected by a child whom she looked after and who showed similar lesions. Two other children and a servant in the same household also showed the same kind of eruption. He also mentions that somewhat later he saw two similar cases in children who belonged to different families but were in the habit of playing together. He points out in his *Atlas* that " the peculiar circumstances which distinguish this species of molluscum from the common excrescences of that name are its contagious quality and the emission of a milky fluid from an imperceptible aperture in the apex of most of the tubercles on pressure, by means of which fluid it is probable that the disease is inoculated."

Again in his *Practical Synopsis of Cutaneous Diseases* he states that " milky fluid issued from the tubercles and may be presumed to be the medium of the contagion." Bateman therefore quite recognised from the first the contagiousness of the condition, and that the milky fluid from the lesions conveyed the infection. It is interesting to note that Bateman was a graduate of Edinburgh University. He was born at Whitby in Yorkshire, where his father was a surgeon. He began the study of medicine in London, then came to Edinburgh, and after continuing his studies there graduated M.D. of Edinburgh University in 1801. He practised in London and was one of the

pioneers in Dermatology.   Shortly after publishing his description of molluscum contagiosum Bateman mentioned his cases to Professor John Thomson, who was the first Professor of Pathology in Edinburgh University, occupying the Chair from 1831 to 1842.   Thomson evidently had kept the condition in mind, because shortly thereafter he told Dr Paterson of Leith (to whom I shall refer again) that he had seen three cases of molluscum contagiosum in a family living in the Canongate in Edinburgh and other three cases (one adult and two children) at a farm in the vicinity of Edinburgh.   Professor Thomson, therefore, was quite familiar with the condition.   After a fairly thorough search I cannot find any record of these cases having been published or even referred to in his lectures to his students.

The next report of cases of molluscum contagiosum is in the *Edinburgh Medical and Surgical Journal* of 1841 by Professor William Henderson.   There he mentions three cases of molluscum contagiosum which he had seen in 1834, all in one family, residing in Jamaica Street, Edinburgh, and a fourth case in a child in the habit of associating with these three, and he emphasises the obvious contagiousness of the condition.   A fifth case is also described in a boy eight years of age who died of pulmonary and abdominal tuberculosis.   In the description of the post-mortem on this child he quite rightly regarded the molluscum contagiosum as unconnected with the tuberculosis.   From this case he obtained abundant material for investigation.   He shows figures of molluscum bodies which he calls "globular cells of which the atheromatous matter, which can be squeezed from the tubercle, chiefly consists."   He also dissected out a lesion from the subjacent tissues and described its lobulated character and suggested that the atheromatous secretion was the means by which the disease was propagated.   He tried to inoculate the condition on the human skin by means of material squeezed from lesions, but was unsuccessful.

Those of you who are interested in the personality of medical pioneers will find some interesting details about Professor William Henderson in Comrie's *History of Scottish Medicine*.   He succeeded Professor Thomson in the Chair of Pathology in the University in 1842 and occupied the Chair for twenty-seven years.   He published a number of clinical studies on diseases of the heart and large blood vessels, and was one of the first to use the microscope in the study of changes in the internal organs, describing in 1841 the appearances in the lung in pneumonia and other pathological conditions.   He is also reputed to have been the first to distinguish between typhus and relapsing fever, both very important diseases of the time.   But he is chiefly remembered by the storm raised in 1845 when he went over to Homœopathy.   On that account he had to resign his appointment at the Infirmary, where he was a physician and taught clinical medicine.   His colleagues, including Syme and Simpson, tried to oust him from the Chair of Pathology, but were unsuccessful.   A controversy raged for about eight years, and in reply to attacks Henderson published numerous pamphlets upholding his position.   He lived for many years

at 63 and later 61 Northumberland Street, removing in 1857 to 50 Moray Place, and six years before he retired he went to 19 Ainslie Place where he died.

In the same year (1841) as Henderson published his cases of molluscum contagiosum, Robert Paterson, a physician to Leith Dispensary, also published three cases of molluscum contagiosum from which he removed lesions and examined their structure. He described the whitish milky fluid which could be expressed from an irregularly-shaped cavity in the interior of the tumours. He mentions that it is composed of peculiar globules which, under the microscope, are seen to be entirely composed of oblong and ovate nucleated cells. He describes each globule or molluscum as consisting of three layers from within outwards, viz. a central area filled with small-granular material, surrounded by a definite membranous capsule (or as he calls it—a vesicle) and external to that a more transparent membrane which attaches the bodies to each other. He gives the diameter of these bodies as $\frac{1}{1000}$ inch, i.e. $\cdot 25\mu$, which is exactly the size established by modern methods of measurement. Although Paterson gives a fuller description of the microscopic appearances of the molluscum bodies than does Henderson, it is obvious from their respective articles that they had seen each other's cases of molluscum contagiosum and discussed the question of the molluscum bodies together. Henderson and Paterson therefore have the credit of being the first to describe cell inclusion bodies as the cause of disease. Considering that this work was done over a hundred years ago, when microscopic histology was in its infancy and the methods of preparing specimens for microscopic examination were very primitive, it is wonderful how accurate their findings were. It is not so surprising in the case of Professor Henderson, who was a teacher of Pathology, but, in Paterson's case, it is very creditable that a general practitioner in Leith should have done such good work.

HISTOLOGY OF MOLLUSCUM CONTAGIOSUM

The microscopic changes seen in a stained (Hæmatoxylin and eosin) section of molluscum contagiosum are quite characteristic. What is most striking is the great hypertrophy of the epithelial cells, so that the epithelial layer becomes about six times the thickness of the normal. This leads to a bulging upwards to produce the domed lesion and the compression of the skin papillæ by the mass of enlarged cells, so that the growth takes on an appearance superficially resembling a secreting gland. In the early work on this disease the condition was thought to arise from the sebaceous gland or hair follicle, and therefore was described under such names as acne varioliforme, acne molluscoide, sebaceous molluscum, etc. ; but it was later recognised that the lesion had no connection with the skin appendages and that the material, which could be squeezed from the lesions, was not sebaceous-gland secretion. On examining the section from below

upwards, in addition to the increased size of each epithelial cell, one observes that the nucleus is much larger and more distinct than normal. It was noticed by many workers that some nuclei show two or more nucleoli, which vary in size and may sometimes be extruded from the nucleus into the cytoplasm of the cell. This gave rise, at one time, to much discussion and the suggestion that they were intranuclear inclusions. Finlay and Ludford (1926) state, however, that nucleolar extrusion is a phenomenon associated with normal keratinisation in most epithelial cells, and careful examination of the appearances in molluscum contagiosum confirms one in this conclusion. In the cytoplasm of the cells a short distance above the basal layer of the skin roundish, oval or pear-shaped bodies, stained with eosin, appear. These are now generally known as Henderson-Paterson inclusion bodies. They are found in many of the cells, and as the cells grow upwards towards the surface these bodies increase in size, pushing the nucleus to the side of the cell, so that it becomes flattened, crescentic in shape, and stains very darkly. There is usually only one inclusion body in each cell. When one reaches the level of the granular layer of the skin, one sees the large inclusion body surrounded by masses of hypertrophied keratohyalin granules stained very darkly with the hæmatoxylin. The inclusion bodies at this level also frequently show an oval or rounded clear space at one end. This is apparently an air-space. At the level of the horny layer the stratum corneum is well formed, and between its layers lie numerous slightly shrunken Henderson-Paterson bodies. It is rather astonishing to find how, in spite of the presence of inclusion bodies in so many of the epithelial cells, the other uninfected cells, though hypertrophied, go through all the stages of normal keratinisation to produce normal stratum corneum cells without any signs of parakeratosis.

At one time it was suggested that these inclusion bodies were protozoa, and Bollinger and Neisser thought they belonged to the class of Gregarines. Later this view was abandoned, and for many years they were regarded as swollen epithelial cells undergoing a form of hyaline degeneration, but now it is generally admitted that they are the containers of virus elementary bodies, and if one examines them under the oil immersion lens one sees that each inclusion has a kind of outer membrane from which trabeculæ extend into the interior, breaking it up into compartments which are filled with innumerable small granules often called Lipschutz bodies, after Lipschutz, who first described them in 1907. He thought they were protozoal elements and called them Strongyloplasma Hominis, but they are now generally recognised to be elementary bodies similar to those found in other virus diseases. They can just be distinguished with an ordinary oil immersion microscope and look like masses of little granules. It is difficult to say at this magnification what their shape is, but they have been shown under the electron-microscope to be slightly elongated and square-ended. As the inclusion bodies grow older their capsule becomes more and more opaque, so that from the stratum granulosum

upwards it is no longer possible to see the elementary bodies. They can, however, be demonstrated by making films from crushed molluscum bodies and staining them with Giemsa, Paschen or Mann's stain. This virus was first demonstrated to be a filter-passer by Juliusberg in 1905, and this has been repeatedly confirmed since. Finlay found that it retains its vitality in 50 per cent. glycerol for one month. Its size was given by Lipschutz and others as ·25 μ, but van Rooyen estimated it at ·3 or ·35 μ.

Van Rooyen by his micro-dissection experiments has done much to confirm these skin section findings. He showed that the inclusion body could be shelled out of the epithelial cell, leaving a cavity behind. He found it to be oval or pear-shaped, possessing a definite surrounding membrane not attached in any way to the cell cytoplasm. At the broader end of the body the capsule is thick and opaque, whilst at the other end, which is more pointed, it has a thin translucent cap. At this end it is readily ruptured and the contents removed. The contents consist of myriads of minute elementary bodies embedded in a jelly-like substance. Van Rooyen has also shown that the outer covering membrane of the inclusion body probably consists of carbohydrate material, and by micro-incineration methods that it contains more calcium than the surrounding body tissues.

An interesting question arises and much controversy has taken place as to how these and other cell-inclusion bodies are formed. Are they produced from the cytoplasm of the cell as a reaction to the presence of the virus, or are they produced by the virus itself? Although the majority of workers regard them as a cell product, there is a good deal to be said for the opposite point of view. Many organisms are known to surround themselves with a sticky matrix; for example, in Trichomycosis nodosa on the axillary hairs, the condition is due to a streptothrix (Actinomyces Tenuis) producing a sticky matrix which dries into a hard cement-like substance that adheres firmly to the hair. A somewhat similar thing is also seen in most fungus spores. Take for example the Penincillia. The spores at first are quite colourless, and their outline can be clearly seen, but in a day or two they become cloudy and indistinct because of a substance which covers the spores, seems to coagulate and turn green in colour. The same thing happens with cultures of Aspergillus Niger. At first the spore is quite clearly seen, but in twenty-four hours it is completely obscured by a black material which has exuded from it and coagulated so as to form a dense black covering which after a day or two dries and shrivels. Is the capsule of an organism such as the pneumococcus not of similar origin? Only under certain growth conditions is the capsule produced by the organism. Similarly it is suggested that when elementary bodies get into an epithelial or other cell cytoplasm each colony becomes surrounded by a material produced by themselves. This material coagulates to produce the outer capsule and the trabeculæ inside the inclusion body. As the inclusion body becomes older the outer capsule dries more and more till, when (in molluscum contagiosum) it reaches

the surface, the outside is firm and solid because it has dried, but inside, where the matrix is not exposed to the air, it is still of a semiliquid sticky consistence.

There is no evidence of immunity to molluscum contagiosum. Treatment of a few lesions (with carbolic acid or CO_2 snow) does not lead, as sometimes happens with ordinary warts, to the disappearance of untreated lesions. The condition is purely an infection of the skin epithelium, and there is no evidence of infection of internal organs. Van Rooyen attempted to agglutinate the elementary bodies of molluscum contagiosum with the serum of patients suffering from the disease, but was unable to demonstrate any specific agglutinins.

Leber (1913), working in Sumatra, made extracts of excised molluscum contagiosum lesions in normal saline and alcohol. With these he tried to demonstrate the presence of specific antibodies by complement-fixation tests. He did a large series of tests, but failed to get any positive results. He also did skin tests (as in the Tuberculin Pirquet test) with his extract on patients with molluscum contagiosum, and all were negative except one. But as eight out of twelve controls also gave positive results, the reactions were probably non-specific and due to some toxic substance in the extract. Leber claims to have cultivated the elementary bodies from the deep part of molluscum contagiosum lesions in hangdrop preparations of human serum incubated anaerobically. He claims that a visible opacity occurred after forty-eight hours. This was filtered through a Berkefeld filter and the filtrate mixed with fresh serum and incubated. He states that he obtained as many as ten generations of growth in one case in this way. He also states that, in these filtrate cultures, besides minute bodies lying free there were larger round or oval bodies ($\cdot$6-1$\cdot$7 μ in diameter) which increased gradually in size and consisted of minute bodies embedded in a zoogloea-like mass. This work has never been confirmed, and all other workers have failed to culture the virus in either liquid or solid media.

Fowl-pox (sometimes also called contagious epithelioma or canker) has some features in common with molluscum contagiosum, and some of the dermatological text-books state that the two conditions are identical. Fowl-pox is a highly infectious disease of birds, especially fowls, which may show itself in two forms: (1) the cutaneous type characterised by the presence of a vesico-nodular eruption on the unfeathered parts of the bird, especially on the comb, eyelids and wattles; (2) the diphtheritic type in the mouth and throat, causing membranous patches. Not uncommonly both types are present in the same bird. In the skin type the lesions are raised, blister-like nodules which soon become covered with brownish scabs. They enlarge, coalesce into patches and form rather warty masses. On removal of the scab a raw rough bleeding surface is left. The lesions in mild cases are few in number, but in severe cases may be very extensive, covering the greater part of the head. Similar eruption may also be seen on the legs and feet, around the vent and under the

wings. After from three to four weeks the scabs gradually loosen and fall off and the lesions heal. The fowl may show little or no general disturbance, but, if the eruption is extensive, the bird may show listlessness and loss of weight. The diphtheritic type in the mouth and throat is a more serious condition. Raised yellowish patches covered with a diphtheritic-looking membrane are found in the mouth and throat. When the membrane is removed a necrotic bleeding area is found underneath. As the patches grow larger they interfere with eating, swallowing and breathing, the bird rapidly loses weight and in a certain number of cases dies within three to five weeks.

For a long time the skin and diphtheritic types of the disease were regarded as separate infections, and many bacteria were described and incriminated ; but in 1902 Marx and Sticker showed that the causative agent was filter-passing and this was confirmed by Juliusberg (1904) and by many others since then. The fact that birds which recover from the diphtheritic form are immune to the cutaneous type of the disease and vice versa also points to the two conditions being of identical origin.

In the epithelial cells of fowl-pox lesions, numerous rounded or oval inclusion bodies varying greatly in size are found. These were first described as long ago as 1865 by Bollinger and also about the same time by Rivolta, hence they are sometimes designated "Bollinger bodies." Sections of the skin and throat lesions show an enlargement of the epithelial cells with inclusion bodies in the cytoplasm very similar to those seen in human molluscum contagiosum, and the whole lesion shows the same gland-like arrangement of the swollen cells. Except that the inclusion bodies in fowl-pox are more variable in shape, size and number than in molluscum contagiosum, the resemblance of the two conditions is very striking.

It has also been shown that the inclusion bodies in fowl-pox contain very numerous elementary bodies which are often called "Borrel bodies" because first described by him in 1903, this being the first description of any elementary body. Since then much work has been done on these bodies. To show that they are inside and not on the outside of the inclusion body Woodruff and Goodpasture (1929) isolated a fowl-pox inclusion by micro-manipulation and washed it in saline. The washed inclusion produced the disease, whilst the saline used to wash it was non-infective.

Some workers have reported inflammatory lesions in the internal organs of hens dying of fowl-pox, but these are not constant and any changes found are probably due to secondary infecting organisms.

Fowl-pox spreads very rapidly amongst hens, and even after several months it is not safe to introduce healthy hens into a run where fowl-pox has been. The incubation period is five to seven days and the disease runs a course of three to five weeks.

A similar disease to fowl-pox also occurs quite commonly in pigeons—the so-called pigeon-pox. Other varieties of the condition have also been described in turkeys, geese, pheasants, partridges,

hawks, North-American bunting-sparrows and canaries. In all these the lesions are clinically and microscopically similar to those of fowl-pox.

The question naturally arises as to whether all these bird-poxes are due to the same virus. Fowls will take pigeon-pox from pigeons, but pigeons do not often get fowl-pox from hens. Not all strains, which are pathogenic for hens, can attack pigeons. Cross-immunity tests have been made with pigeon, canary and turkey-pox viruses, which go to show that there are probably several pathogenic types of bird-pox virus, so closely related that they are possibly only different strains of the same virus. Seiffert (1943) states that all strains differ in their pathogenicity for different kinds of birds but all strains can soon acquire, by cross-infection, a higher pathogenicity for the new host. At the same time they usually lose their pathogenicity for the original host, but can reacquire it by retransmission through it.

Immunity, in cross-infections, shows a corresponding behaviour to that of pathogenicity. Fowls which have survived an attack of fowl-pox are immune to further infection for a considerable time. Arising from this fact, young fowls have been treated with a vaccine to protect them against fowl-pox. Doyle (1930) introduced a vaccine consisting of dried pigeon-pox crusts suspended in glycerolised saline. This vaccine has been used fairly extensively in and around Edinburgh during the last few years, and the incidence of fowl-pox has been markedly reduced.

Other vaccines, such as glycerolised egg-propagated fowl-pox virus, are also being tried, and it is hoped by this means to get even better results in the future.

In addition to these bird-poxes, molluscum lesions, showing microscopically typical cell-inclusion bodies, have been described in amphibians (lizards and toads), but, as they have all been published in unobtainable foreign journals, I have been unable to get details of them.

What is the relation, if any, between molluscum contagiosum and bird-pox? The clinical lesions in the two conditions are quite different. Molluscum contagiosum shows, after a long incubation, a slowly developing solid lesion with hardly any signs of inflammation, whilst bird-pox has a short incubation period of a few days and shows very inflamed vesico-pustular lesions with marked inflammatory reaction. Clinically, therefore, there is no great resemblance in the two conditions. It is quite otherwise, however, when one compares the microscopic appearances. Both show similar collections of hypertrophied cells arranged in a manner suggesting a secreting gland. In both, the cells contain numerous large inclusion bodies which stain readily with eosin. In molluscum contagiosum they are oval or pear-shaped and have a very definite capsule. In fowl-pox they have not such a definite shape, vary more in size and are more often multiple than in molluscum contagiosum. The elementary bodies in both conditions are filtrable, approximately of the same size and of the same shape so that they are indistinguishable morphologically. But in biological characters they

are quite different. There is no record of human beings ever contracting molluscum contagiosum from handling hens, pigeons or other birds suffering from bird-pox. As these diseases are fairly common in poultry, this would certainly happen often if the diseases were due to the same virus. Conversely, fowls and pigeons do not get infection from human molluscum contagiosum, so that, although the two conditions resemble each other microscopically, they are quite different diseases due to different viruses.

Molluscum contagiosum is pathogenic to man only and has never been known to infect any animal. But there is one record where an animal was supposed to have infected a human being. This case was published in 1895 by Jonathan Hutchinson in his " notes of clinical cases." A young woman was shown by Mr Hitchins at a clinical meeting with typical lesions of molluscum contagiosum on the chest and shoulders. Her dog also had tumours scattered over its back and sides said to be exactly like human molluscum contagiosum. When excised and examined these were also said to show typical molluscum bodies. The lesions on the dog had been present for two years and those on the young woman for only two months. From this it was inferred that the woman had been infected from her dog. As no other similar case has ever been recorded in dogs, and as the lesions on the woman's skin were on the covered parts and not on the hands and arms, it is not likely that she caught the infection from the dog. There is therefore some doubt as to whether the lesions on the dog really were true molluscum contagiosum.

TREATMENT

The treatment of molluscum contagiosum is very satisfactory. The best method is to squeeze out the contents of each lesion and insert a drop of pure carbolic acid on a probe or dental burr. Usually one application will cure every lesion of ordinary size, leaving no scar. Very early minute lesions can be cured by simply touching them with the pure carbolic.

After all the lesions have been treated the patient should be warned to keep a look-out for further lesions which may be incubating and are not yet visible. Lesions can be snipped off with curved scissors or excised by the knife, but that leaves a scar. I have tried freezing with CO_2 snow as for warts, but it is not as satisfactory as carbolic acid. X-rays will cure the lesions, but are difficult to apply when the eruption is widely scattered. They are only indicated where there are large plaques of closely aggregated lesions.

If the lesions are secondarily infected and suppurating they should be treated with boracic starch poultices or other antiseptic soaks. Over one hundred years ago Henderson and Paterson treated their cases by applying silver nitrate with good results. Henderson gave arsenic by the mouth and found that, although it seemed to stop the growth of lesions, it did not cure them.

Ghosh (1934) in India made a vaccine by emulsifying a molluscum contagiosum lesion, filtering and killing the virus with formalin. He gave intradermal injections of the filtrate twice a week in gradually increasing doses. In six cases so treated all were cured before the sixth injection of the vaccine. Brain, in London (1937) made a similar vaccine, but had no therapeutic success with it. Sakurane of Japan (1908) says that molluscum contagiosum can be cured by the internal administration of a decoction made from the seeds of Coix lachryma (Job's tears). This plant is an ornamental grass found widely in tropical Asia. Sakurane says it will cure molluscum contagiosum usually within two weeks, the lesions becoming smaller, darker in colour, shrivelling up and dropping off. He also states that this drug is well known in Japan and has long been used in the treatment of molluscum contagiosum.

In conclusion one can summarise the present position of our knowledge of molluscum contagiosum as follows :—

1. Molluscum contagiosum is a contagious disease due to infection of the epithelial cells of the skin with a filtrable virus elementary body.

2. This virus elementary body is contained in the cell-inclusion commonly known as the " molluscum body."

3. The diagnosis is usually easy, but if there is any doubt, it can be established by microscopic demonstration of these molluscum bodies.

4. Molluscum contagiosum only affects human beings and is an entirely different disease from contagious epithelioma of birds (so-called bird-pox), which is due to a virus resembling that of molluscum contagiosum only in its morphology.

5. There is no evidence that an infection with molluscum contagiosum produces any immunity.

6. The treatment is easy and satisfactory and a rapid cure can be guaranteed.

7. Except that the disease is undoubtedly often spread by public bathing establishments, practically nothing is known (and this applies equally to other virus conditions) as to how the virus behaves when apart from the human body.

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PROBLEMS IN ARTERIAL SURGERY *

By F. ALBERT

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MORE than twenty-two years ago I published a long series of experimental and clinical studies on " les troubles physiopathiques post-traumatiques " (post-traumatic dystrophy), which comprise a complex group of reflex disorders following injuries to the limbs, and especially injuries to the joints (wrist, ankle, fingers or toes). All cases, severe or not, are characterised by the presence of vasomotor disturbances and by pain. Nearly any form of injury to an extremity may be followed by " physiopathic " disorder. Some disappear spontaneously, others persist and become more and more severe. The disability can be very important. The syndrome, when complete, includes sensory and motor disorders, diffuse, intractable and often agonising pain, loss of muscle tone and atrophy of muscle, alteration in the sensitivity of the skin, and, above all, vasomotor, thermal and trophic disorders.

All our experimental work was carried out by the technique known as " Nolf's method."

SUMMARY OF NOLF'S TECHNIQUE.—A dog, anæsthetised with chloralose, is fixed on its back. One carotid and both femoral arteries are exposed and ligated. It is necessary to wait for about one hour until the collateral circulation is established. A glass cannula, containing sodium citrate solution, is then inserted into the central end of the carotid and into the peripheral end of each femoral artery. The cannula is connected with a registering manometer, by a rubber tube also filled with sodium citrate solution. The carotid manometer registers the variations of general pressure, and the femoral manometers give the peripheral pressure variations in the hind leg, which are an indication of all the vasomotor changes in that limb. According to Nolf's observations, every fall of pressure in the femoral manometer corresponds to vasodilatation in the territory of the corresponding limb, while every rise of pressure corresponds to vasoconstriction. We shall see later the limitations with which this interpretation should be regarded. Sometimes we register the general pressure in the central end of the axillary artery instead of in the carotid, to avoid interference with the carotid sinus.

By this technique we were able to show, after much experimental work, that the origin of all post-traumatic physiopathic disturbances is to be found in the vasomotor reflexes evoked by injuries, however

* A Guest Lecture in Surgery delivered at the University of Edinburgh on 4th March 1946.
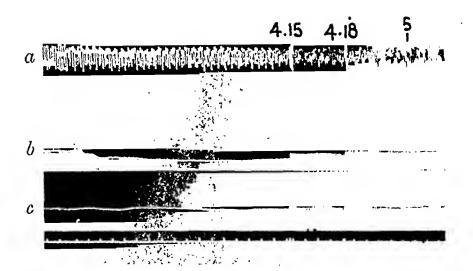
FIG. 1.—Dog, 15 kg., prepared according to Nolf's technique. (*a*) manometer in central end of carotid artery; (*b*) manometer in peripheral end of left femoral artery; (*c*) manometer in peripheral end of right femoral artery. Injection of left knee (anæsthesia such as to prevent any painful reaction or defensive movement). A fall of peripheral pressure on the left side is immediately registered, corresponding to a localised vasodilatation in this limb.

slight, of all articular and mainly peri-articular tissues (Fig. 1). By a process of elimination (Fig. 2), we noted that these reflexes persist in spite of proximal section of the nerves of the limb (Fig. 3), of section
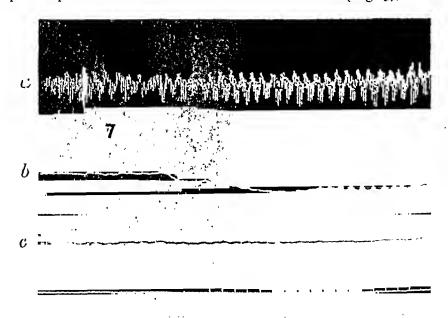
FIG. 2.—Dog, 12 kg. Same technique. All the nerves of the left paw have been divided. 7: injection of left knee. Despite division of all the nerves, the same vasomotor and vasodilator reactions are registered. Exactly the same response is obtained after division of all the nerve roots.
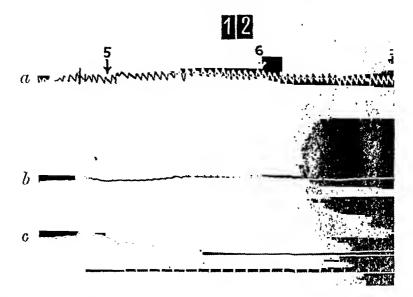
FIG. 3.—Dog, 27 kg. Same technique. Incision and complete removal of marrow. 5-6 : pinching of right patellar tendon. Identical response.

of the nerve roots and the sympathetic chain, even of section or extirpation of the medulla, but that, on the other hand, they disappear after degeneration of the nerves of the limb (Fig. 4) ; they are axon-reflexes.
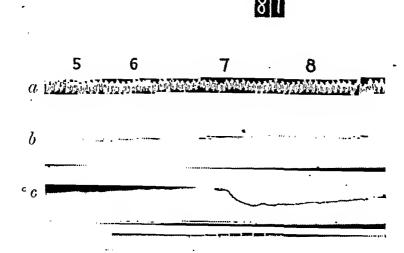
FIG. 4.—Dog, 15 kg. Same technique. A fortnight before this experiment, the nerves of the left paw were divided and resected at a certain level. The peripheral ends degenerated since this first intervention. Actually, injection of the left knee no longer gives a further fall of pressure (5-6), while injection of the right knee (7-8) still gives the same response.

Studying, then, the influence of local anæsthetics on these post-traumatic axon-reflexes, we observed that, while these vasomotor reactions persist after section of all nerves at the base of the limb, blockage of the same nerves at the same level by novocaine suppresses them entirely (Fig. 5). Thus nerve block with a local anæsthetic is not really, as we thought before, a physiological section, but all the affected neurons are functionally put out of use, as if they were momentarily degenerated. This is very clearly proved by the fact (Fig. 6) that a spinal anæsthetic causes all those vasomotor reactions to disappear, except when the nerves have been previously cut at the base of the limb. In this case, the post-traumatic axon-reflexes persist
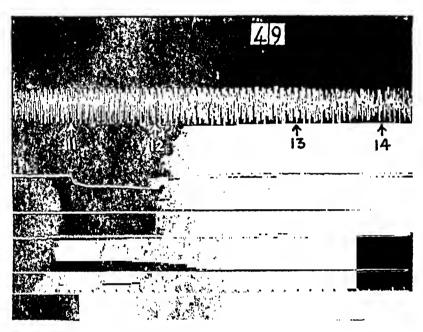
FIG. 5.—Dog, 18 kg. Nerve block of the right paw with 4 per cent. scurocaine, at the same level as that for division. 11-12: pinching of left patellar tendon: normal response. 13-14: pinching of right patellar tendon: no response now.

on the denervated side, and disappear on the side where the nerves are intact. Section of the nerves stops, as a barrier, the action of spinal anæsthesia on the peripheral part of the axons. Lastly, local anæsthetic infiltration, at the site of the injury, also prevents all vasomotor reaction. Still more surprising is the fact that blockage of the trigeminal nerve (at the level of the Gasserian ganglion) may prevent much more violent reactions, such as the severe conjunctival response to instillation of mustard oil into the eye.

This experimental study was the basis and the origin of all preventive or curative treatment by the infiltration of novocaine, which was so widely used throughout the world. In the application of our experimental work, Leriche published first his clinical results of the treatment of ankle strains by anæsthetic infiltration, and since then the method has been known under his name. We use it not only for

joint injuries, but also for a large number of painful diseases, and we have had most interesting results.
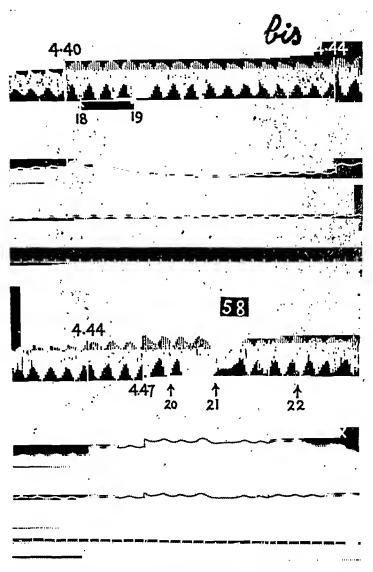
FIG. 6.—Dog, 16 kg., 500 gr. Spinal anæsthesia (10 mgm. scurocaine in 4 per cent. solution without adrenalin), after division of the left sciatic and femoral nerves. Pinching of left patellar tendon (18-19), on the side of the divided nerves : normal response. Pinching of right patellar tendon (20-21), on the side of the intact nerves : no vasomotor reaction. Spinal anæsthesia suppresses completely all axon reflexes in the territory of neurons affected by the anæsthetic. On the other hand, preliminary division of the nerves on one side stops, like a barrier, the effect of spinal anæsthesia.

In the same way it seemed to us particularly interesting to elucidate the vasomotor responses to different forms of vascular injury and disease, whether arterial or venous. Clinically it has been known

for a long time that an arterial injury which is followed by local thrombosis or by any other irritation of the wall of the artery, may cause vasomotor reflex disorders in the corresponding limb. This spasm of the vessels sometimes seriously threatens the vitality of the limb. However, resection of the injured fragment of the artery, or blockage of the appropriate sympathetic ganglia, may prevent these vasomotor reactions and save the leg. We observed similar facts during an experimental study on arterial embolism. The same disorders can be observed in arterial spasm, spontaneous or traumatic, and infiltration of the nerves or ganglia with local anæsthetic, or, sometimes, the interruption of nerve pathways by spinal anæsthesia, gives interesting and rapid improvement. Intra-arterial anæsthetic injection is particularly useful when the spasm does not entirely obliterate the vessels. This means also that in order to avoid pathological vasomotor reflexes, most of our operations will benefit by local anæsthetic block, even when general anæsthesia is used.

And so we come back to the anoci-association that Crile imagined and advised many years ago, without explaining its true physiological basis. That is the reason why this interesting technique had been practically forgotten, at least in our country.

It seemed to us that, in order to trace the origin of these reactions, it might be advisable to obtain an accurate appreciation of the peripheral vasomotor reactions which follow a simple lesion, such as obliteration of a main vessel.

Ligature and Arterial Compression

By means of the same technique, we observed the following facts :—
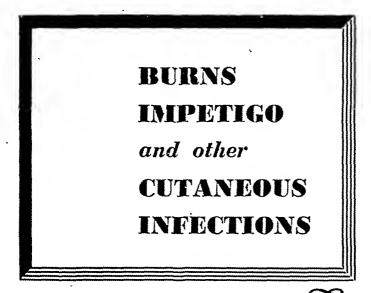
(1) Compression or simple ligature of a main artery regularly causes, not vasoconstriction, but marked and prolonged vasodilatation in the corresponding limb.

(2) This vasodilatation is still more marked if the vessels have been previously constricted.

By division of the nerves of the limb and inactivation of the corresponding sympathetic chain by the use of drugs which paralyse the sympathetic system, or by blockage with a local anæsthetic, we found that vasomotor responses to arterial compression or to ligature are absolutely independent of the central and peripheral nervous systems. Anæsthetic infiltration of the nerves and of the sympathetic chain on the same side alters slightly the vasomotor response. Perhaps some axon-reflexes take place in the sympathetic post-ganglionic neurons. But in the same experiments we found that after a short time of adaptation, the vasomotor response became identical with what it was before the anæsthetic infiltration (Figs. 7 and 7A).

It seems that the main cause of the vasomotor reactions is to be found in physico-chemical modifications of the peripheral blood and interstitial fluids, under the influence of a cellular metabolism impaired

by arterial obliteration. This is in agreement with the observations of Krogh and Lewis. We have also been able to demonstrate in man the presence of vasodilator agents in the venous blood of a limb affected by gross peripheral sympathetic disorder.

Nolf's method gives only a rough indication in the form of a fall or rise of peripheral pressure. It is, however, possible that this increase or fall in pressure is a summation of the various and even opposite vasomotor reactions in different parts of the limb, of which only the dominant is registered. Arteriography probably gives a more adequate localisation of the vasomotor changes.

FIGS. 7 and 7A.—(a) carotid artery; (b) its base line; (c) peripheral end of left femoral artery; (d) its base line; (e) peripheral end of right femoral artery; (f) its base line. Dog, 14 kg. 100 gr., chloralosane, 1 gr. 40 mgm.

Fig. 7.—1-2: the lower part of the aorta was occluded; usual fall in successive steps; on reopening, the pressure rises very slowly. After an initial stop, the drum is started again, at first two minutes, then regularly one minute, after stopping. At A, the left lumbar sympathetic chain is anæsthetised with 4 per cent. syncaine, after first having been freed. Immediately afterwards, at 3-4, occlusion of the aorta causes a slighter fall in the left (c), but what is particularly striking is that when it is reopened the peripheral pressure mounts rapidly, even above the initial level.

Fig. 7A.—Several minutes afterwards, despite fresh anæsthesia of the left chain, occlusion of the aorta gives a curve identical with the first, obtained before anæsthetising the sympathetic chain.

TECHNIQUE.—Thorotrast is injected with a syringe, through a large cannula fixed in the central end of the sacral aorta. The thorotrast, directly mixed with the blood of the inferior part of the abdominal aorta, is drained in a uniform way into the vessels of both limbs.

A preliminary arteriogram is taken on the normal animal (Fig. 8) to show whether the vascular tree is symmetrical and comparable in both legs. The main artery of one limb is then obliterated for a few minutes, after which the compression is released. Arteriography is again performed. *We regularly registered a very intense vasodilatation spreading to the whole of the corresponding limb.* These

arteriographic findings entirely confirm our previous results obtained by Nolf's method. They show also that the vasodilatation extends to the whole arterial network of the limb.

In order to measure comparatively the importance of vasomotor reactions to arterial obliteration, a left lumbar ganglionectomy was performed on the same dog. After a first arteriogram registering the result of this resection of the lumbar ganglia, the right iliac artery was compressed for a few minutes. A subsequent arteriogram (Fig. 9) shows that the vasodilatation produced on the right side by simple arterial compression is at least as intense as that on the left side where lumbar ganglionectomy had been performed. There is, of course, a difference. Ganglionectomy induces if not a definitive at least a much more prolonged vasodilatation. The arterial compression gives only a momentary vasodilatation, but we can reproduce it as often as we like.

CLINICAL APPLICATIONS.—When used for treatment, arterial compression is done with the fingers by the nurse or by the patient himself. It is always applied to the main artery, as high as possible. The degree and the duration of the vasodilatation are proportionate to the duration of arterial compression (five to fifteen minutes), and to the intensity of previous peripheral vasoconstriction. In cases of post-traumatic dystrophy, for instance, the limb quickly becomes red and warm and the patient himself notices an improvement in his peripheral circulation. After ligature of the main artery of a limb, peripheral vasodilatation increases progressively, indicating impairment of the arteriolar and capillary pressure and of the viability of the tissues. Further, arterial compression has many therapeutic applications wherever peripheral vasodilatation is required. We use it daily in the treatment of :—

(1) *Post-traumatic vasomotor disorders*, where the results are often remarkable and extremely rapid, especially when this therapy is applied in early stages of the disease.

(2) *Surgical œdema* of traumatic origin. Here the results are less dramatic.

(3) *Traumatic osteoporosis*. In the painful forms, pain is often fairly rapidly relieved and disability ceases at the same time. Simple local infiltrations of novocaine produce sometimes the same lasting good results. Both forms of treatment may be combined.

(4) *Delayed union of fractures*.

(5) *Circulatory disturbances* following endarteritis, mainly in juvenile forms (Buerger's disease) where unexpected successes are sometimes achieved.

VENOUS COMPRESSION AND LIGATURE

Arteriographic study of arterial compression fully confirms the statements previously obtained by Nolf's method. A similar study

of venous compression revealed some rather unexpected details. Nolf's method had previously enabled us to observe the following facts. Venous compression is rapidly followed by a rise of peripheral pressure, the result, we considered, of an active vasoconstriction added to the simple hydrostatic barrier. Peripheral pressure is indeed sometimes greater than central (Fig. 10). This increase of pressure is nearly always preceded by a slight fall, which, however, is only
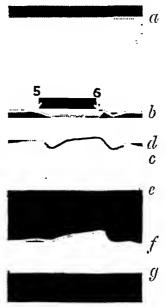
FIG. 10.—(a) time in seconds ; (b) central end of axillary artery ; (c) its base line ; (d) peripheral end of right femoral artery ; (e) its base line ; (f) peripheral end of left femoral artery ; (g) its base line. 5·6 : vena cava closed. Note the difference in vasomotor responses on the right and left sides. The right paw is originally more vasoconstricted than the left.

momentary ; there is then a quick rise of pressure which may surpass the initial level. This transitory fall of pressure appeared to us an important fact, but difficult to interpret ; it proved, however, the vasomotor origin of part of the registered phenomena (Fig. 10).

Complementary experiments show that one or other of these vasomotor deviations would become dominant according to the pre-existing vasomotor conditions. When, just before, a strong peripheral vasoconstriction is induced either by denervation of carotid sinuses and section of the depressor nerves, or by intra-arterial injection of a small dose of epinephrine (adrenaline), the response to venous compression is very different, the fall of pressure being much more marked and the subsequent increase of pressure being later and less marked (Figs. 11 and 12). If we evoke the inverse phenomenon, i.e. a peripheral vasodilatation (by intra-arterial injection of a small dose of histamine, for instance), at the moment of venous compression, we do not see any fall of pressure (Fig. 13), and the increase of pressure
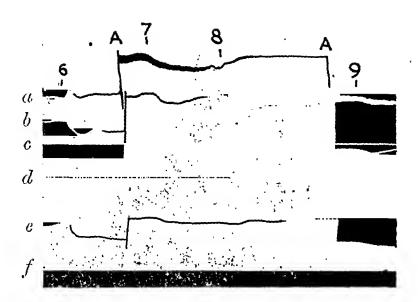
FIG. 11.—(a) central end of axillary artery; (c) its base line; (b) peripheral end of left femoral artery; (f) its base line. To the left (at A) the two carotid sinuses were denervated and the two nerves of Cyon divided; a very great rise in the three manometers will be observed. 7·8: closure of right common iliac vein. 8: vein opened: marked fall of pressure with very moderate rise.
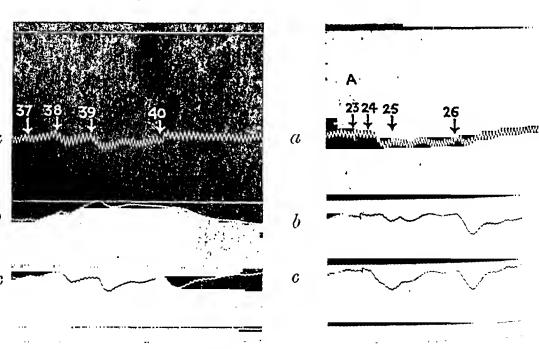
FIG. 12.—(a) central end of carotid artery (b) peripheral end of left femoral artery; (c) peripheral end of right femoral artery. 37-38: injection of 1 c.c. adrenalin, 1/10,000 solution, into the central end of the left femoral artery. Marked rise of peripheral pressure in the left paw. During this rise, between 39 and 40 the vena cava is occluded. Note difference in vasomotor reactions on the left and right sides.

FIG. 13.—Same legend. 23-24: injection of ¼ c.c. histamine, 1/10,000 solution, into the central end of right femoral artery. 25-26: occlusion of vena cava.

appears immediately. The combination in normal dogs of both reactions (fall and then increase of pressure) was a great help in recognising the increase of pressure to be a phenomenon of active vasoconstriction associated with the hydrostatic barrier. On the other hand, it was impossible by Nolf's method to elucidate the real cause of the initial fall of pressure. We thought, at that time, that vasoconstriction was preceded by a short period of vasodilatation, as is sometimes observed in the course of some pharmaco-dynamic effects (small doses of epinephrine, for instance). Similarly, in arterial compression, the vasomotor responses to the venous obliteration persist in spite of the experimental elimination of all innervation of the limb. Here again perhaps some axon-reflexes may play a part, but in a very secondary way. The type of vasomotor reaction is mainly conditioned by the previous vasomotor state of the limb.

Arteriographic study of venous compression has shown that the reality is quite different. Figs. 14 and 15 illustrate quite clearly what occurs in a limb after venous compression. As we expected, the vasomotor response is complex. But instead of following each other, the two phenomena occur together. Vasoconstriction affects the main arterial tree, the large vessels being slightly constricted, smaller ones sometimes obliterated, while the very small ones are dilated. This is proved by the fact that when the radiogram is carefully examined the soft parts are more opaque, with a particularly cloudy appearance which, when examined with a lens, is shown to be caused by a multitude of dilated small vessels. This is the characteristic radiological picture of venous compression, produced by this technique only. If we compare these arteriographic observations with the facts we previously observed by Nolf's method, we come to the following conclusions. The fall of initial pressure, after venous compression, corresponds undoubtedly to vasodilatation of the small vessels. This vasodilatation is thus the first reaction to venous compression, but contrary to what we had first thought, it persists in spite of the secondary rise of pressure. This rise results partly from the simple hydrostatic barrier, of course, but also and mainly from constriction of the whole main arterial area. Venous compression enables us to achieve a very characteristic vasomotor complex.

It has been known since the war of 1914-1918 that ligature of the companion vein improves the results of ligature of a main artery, and thus reduces ischæmia and prevents or limits gangrene. Besides the inadequate blood supply, the main danger resulting from obliteration of the main artery in a limb seems to arise mostly from the steadily increasing fall of peripheral pressure in consequence of the vaso-dilatation it brings about. The vasoconstriction produced by venous ligature brings this pressure back to a more normal level. Because it is limited to the large vessels while the arterioles and capillaries are dilated, it succeeds in preserving and even in improving the nutrition of the tissues.

Experimentally, if the collateral circulation is limited by ligation of the saeral aorta, if the main artery is ligated on one side and the artery and vein on the other, there is a progressive fall of peripheral pressure while the pressure rapidly rises and after a short time respiratory and eardiac oseillations reappear. This is still more clear when the middle sacral vein is tied at the beginning of the experiment.

Here we undoubtedly reach one of the essential facts of peripheral vasomotor reaetion : that vasodilatation or increase of blood supply registered in a limb does not neeessarily improve the nutrition of the tissues. Similarly, vasoeonstriction registered by our usual technique does not inevitably correspond to deficient nutrition. The main point, whieh is also the delieate point, is to grasp what happens in the tissues themselves at the level of the small vascular ramifieations.

This important part of our experimental study on vaseular reactions' was undertaken in my laboratories with a set of perfectly ealibrated thermoeouples which register photographieally. The work eould not be completed beeause, during the war, these instruments had to be kept stored out of danger from air attack. There is, of eourse, no need to ligate the companion vein in all eases of ligature of the main artery. But there is a point of real importance in our statements, which is that the vasomotor reactions to ligature or obliteration of the vein are quite independent of the nervous system, either central or peripheral. Patients may therefore benefit from these vasomotor reactions, even when one or all of the nerves to the limb are out of use. The main indication for ligature of the companion vein is in cases of very large injuries, even with combined arterial and venous lesions, where other technique for inducing peripheral vasodilatation beeomes ineffective.

In our clinic we have used venous compression as well as venous ligature. In the lower limbs the former was easily achieved in Scarpa's triangle, just medial to the femoral artery. Where artery and vein are situated close together, experimental study revealed that moderate compression of the vascular bundle, with eonservation of the peripheral pulse, gave the same vasomotor responses as single eompression of the vein. We have used venous compression mainly in eases of endarteritis with obliteration of the main artery of the limb, where peripheral gangrene is imminent or is just beginning. It is sometimes possible rapidly to limit early gangrene ; the limb becomes warmer, the extremities are better eoloured ; pain decreases and often disappears after only several days of treatment. Venous compression might possibly find an interesting application in tubereulosis of bones and joints, but we do not want to give a definite opinion about this, because the question is still under consideration.

Thus experimental surgery can throw some new light on our physiopathologieal coneeptions, and give us useful indications for the interpretation of certain particularly complex phenomena. It can also supply us with interesting data about surgieal therapy.

HIGH BLOOD PRESSURE *

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ARTERIAL hypertension is a common clinical finding in most forms of medical practice. It may be an integral part of a variety of renal, vascular, endocrine and neurological disorders. In each such instance the visceral disease is regarded as the cause of the hypertension, and indeed in many instances the cure or relief of the visceral disease, if achieved, is accompanied by a return of the blood pressure to normal levels. When no such organic disease is discernible as the cause arterial hypertension graduates by default into the ranks of diseases with the title of essential hypertension, and we must still, for practical purposes, look upon it as a disease entity rather than as a feature of some other underlying condition. This in no way denies the accepted academic belief that a basic lesion will eventually be disclosed. When this happens essential hypertension will join all its cousins as only an outstanding clinical feature of some other pathological process. Essential hypertension may indeed turn out to be not one disease but a variety of diseases.

Essential hypertension, however, constitutes by far the most important of all forms of hypertension, accounting for 80 to 85 per cent. of all cases of hypertension. It has been estimated that one-fifth of the population is hypertensive, and there is little doubt that, as Cabot wrote in 1926, " Hypertension is more common than all other forms of heart disease put together." Essential hypertension, or rather its effects on heart, brain or kidneys, probably constitutes the most important single non-traumatic cause of morbidity and death after the age of forty.

We remain in ignorance of the cause of this common disorder. Although the circle of the light of knowledge on this subject has widened rapidly in the past decade, it has not yet illuminated the most important corner of the room. As the result of the brilliant research during the past ten years or more of Goldblatt in the United States and Houssay in South America, and many others, much information is now available regarding the mechanism of production of renal hypertension. Renal ischæmia, induced experimentally by partial constriction of the renal artery, is followed by sustained hypertension which is not prevented or cured by denervation of the kidney, section of the splanchnic nerves, or section of the anterior spinal nerve roots. This hypertension is due to a direct humoral action upon the

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* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 16th January 1946.

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arterioles. The blood pressure of a non-hypertensive nephrectomised animal is elevated when an ischæmic kidney from a hypertensive animal is transplanted into it. Transplantation of a normal kidney does not affect the blood pressure. Plasma from the vein of an ischæmic kidney has a marked vasoconstrictor effect.
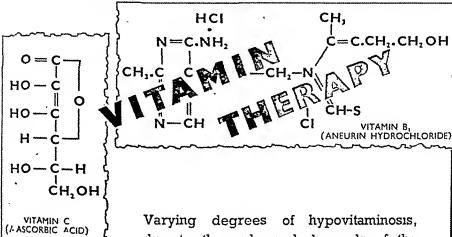
Purified preparations of the pressor substance (commonly known as renin) are inactive, but are reactivated when added to plasma. Renin with renin-activator has been called angiotonin, and this has been isolated in crystalline form. Various experiments have shown that normal kidney tissue forms a substance which antagonises or inhibits angiotonin, and such a " renin inhibitor " has been prepared, has been shown to be effective by oral administration in lowering the blood pressure in hypertension and has given encouraging results in a few human cases.

In chronic nephritis in human beings, renal ischæmia results from the readily observed and well-authenticated vascular narrowing. In unilateral renal disease such as chronic pyelonephritis associated with hypertension, removal of the diseased kidney is followed by a fall in the blood pressure to normal.

The burning question is whether and how far this experimental work on renal hypertension is applicable to human essential hypertension. That the hypertension is due to peripheral vasoconstriction is accepted, but the cause of this vasoconstriction is unknown. It has been observed histologically that the kidneys of hypertensive patients show arteriolar lesions of endothelial hyperplasia, medial hypertrophy and hyaline degeneration of the intima which non-hypertensive kidneys do not show, and yet the arterioles in other sites do not show this difference between hypertensive and non-hypertensive cases. It may therefore be that renal arteriolar constriction is the primary factor with renal ischæmia and hypertension following, even though impairment of renal function does not occur until late in the disease. However, even if this is the mechanism behind essential hypertension the original cause of the renal arteriolar constriction remains to be elucidated. The striking lability of the blood pressure in the earlier phases, the excessive rises which result from emotional or other stimuli, and the great reduction which may follow rest and sedation are strong arguments against a fundamental renal cause. Heredity, constitutional factors such as obesity, endocrine disturbances such as the menopause, nervous factors such as emotional strain may one or all be involved.

Essential hypertension does not arise suddenly except in the rare form of " malignant " hypertension. The much more common benign form develops slowly over many years and its progress may be divided into stages. These stages of course merge imperceptibly into one another and the rapidity of progress through them is very variable.

The initial phase is characterised by an unduly labile blood pressure, systolic and diastolic components showing a tendency to rise temporarily

FIG. 8.—Normal arteriogram. The arterial network is rather vasoconstricted. (By kind permission of the *Proceedings of the Royal Society of Medicine*.)
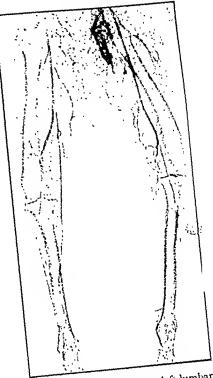
FIG. 9.—Same animal after left lumbar ganglionectomy and compression of the right common iliac artery for six minutes. (By kind permission of the *Proceedings of the Royal Society of Medicine*.)
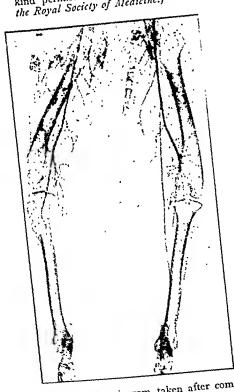
FIG. 14.—Arteriogram taken after compression for six minutes of right common iliac vein. There is vasoconstriction of the large vessels and dilatation of all the small vascular branches. (By kind permission of the *Proceedings of the Royal Society of Medicine*.)
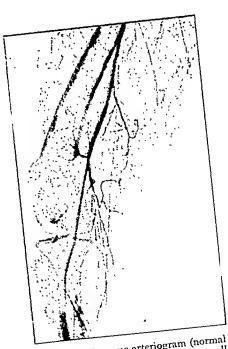
FIG. 15.—The same arteriogram (normal size), which shows details of the small vessels. (By kind permission of the *Proceedings of the Royal Society of Medicine*.)

FIG. 1.—Molluscum bodies from M. contagiosum in Liq. potassae. High power. ×400. (Note large oval bodies filled with minute elementary bodies.)

FIG. 2.—Molluscum bodies from section of M. contagiosum filled with elementary bodies. Oil immersion. ×1000.

FIG. 3.—Elementary bodies of M. contagiosum. ×1200. (Courtesy of Dr van Rooyen.)

FIG. 4.—Section of hen skin showing fowl pox. Low power. ×50. (Note inclusion bodies in epithelial cells.)

into zones of frank abnormality, such as 150-160/95-100 mm., while at other times subsiding to levels which are commonly regarded as normal, such as 130/80-85. The elevations may take place during periods of emotional tension, but are also evident under the stimulus of cold, for the hypertensive or " prehypertensive " subject frequently exhibits an excessive reaction to the pressor effects of cold applied to the extremities, the systolic pressure rising by more than 20 mm. and the diastolic by more than 15 mm. The specificity of the cold pressor test for early hypertension has been questioned. The lower levels are attained during quiet rest, or sleep, and for considerable periods of each day the heart and arteries are not faced with any increased loading. There is considerable possibility that normal blood pressures may be recorded on at least some of a series of routine examinations. It would appear that the vasoconstriction responsible *for the rises in blood pressure is due* to increased nervous tone, since rest with or without sedation can be shown to result in a fall to normal levels. The sodium amytal test serves to demonstrate this lability of the blood pressure The patient·is given 3 grains of sodium amytal by mouth hourly for three hours and the blood pressure is recorded before, during, and after this period. The patient may go to sleep and not waken even when the blood pressure is measured or he may lie in a quiet drowsy state. The lowest figures are usually obtained soon after the third dose has been given, and in this early stage of the disease the minimum pressures recorded are well within the normal range.

In this initial stage of essential hypertension there may be no symptoms whatever, and the hypertension may be an accidental observation in the course of examination for some other purpose. Other patients complain of headaches, fatigue, lack of concentration and dizziness. These symptoms are strikingly similar to those of psychoneurosis, and are observable with equal frequency in patients with normal blood pressure. This fact and the common absence of any symptoms at all make it possible that the symptoms are not directly due to the hypertension. An exception may have to be made in the case of headache, for there is experimental evidence that the headache may be due in these cases to stretching of the cranial or cerebral arteries. It need hardly be emphasised that there is no evidence of renal disease or impairment at this stage and no sign of cardiac enlargement.

As the years go by the daily periods of hypertension become longer and the levels higher, though normal pressures are still attained during sleep and under the influence of sedatives. A higher proportion of observations of the blood pressure now show hypertension and the likelihood of observing normal pressures at routine examinations becomes less. However, the peripheral vessels have not yet become organically narrowed but are still spastically constricted. Removal of nervous vasoconstrictor tone by sedation is still capable of inducing normal or nearly normal pressures.

In this second stage again there are commonly no symptoms whatever, though the same apparently neurotic symptoms may persist, and if headache is a feature of the case it may become more severe and more frequent. As a rule, too, signs of the effects of prolonged hypertension are lacking, but early left ventricular enlargement may now be found especially radiologically, and the mitral first and aortic second sounds may be accentuated. Spastic narrowing of the retinal arteries may be seen.

In the third stage the general level of blood pressure is set still higher, *e.g.* 200-250 or more/110-150. The pressure remains elevated during repose and the amytal test induces a modest reduction, or no reduction at all. Permanent narrowing of the peripheral arterioles has now occurred as the result of medial hyperplasia and fibrosis and intimal thickening. There is evidence of the effects of prolonged arterial hypertension. The most easily detectable and the most important of these is enlargement of the left ventricle. In the absence of cardiac valvular lesions left ventricular enlargement in the middle-aged or elderly adult is almost always an expression of prolonged hypertension. Other features are arterial hardening, hypertensive retinitis and slight or moderate impairment of renal function as indicated by an impaired urea clearance test or a lowering of the maximum attainable specific gravity of the urine.

It is common now for patients to notice some diminution in exercise tolerance, but this may be gradual in development and may not attract the patient's attention sufficiently to take him to his doctor or even to interfere with his normal pursuits. The patient who has headaches in conjunction with hypertension continues to suffer from them and the same neurotic symptoms may persist. Cerebral vaso-spastic attacks are quite common. However, in spite of the advanced stage of the disease, there still may be no symptoms whatever.

In the fourth stage breakdown occurs. Here is the irreversible end result of years, maybe decades, of arterial hypertension. A cerebral or coronary vascular accident may suddenly kill a patient who has not previously complained of any symptoms, and it is only at autopsy that evidence is obtained of preceding prolonged hyper-tension. However, nearly one-half of hypertensive patients eventually exhibit congestive cardiac failure with or without auricular fibrillation or other cardiac arrhythmia, and succumb after a variable period of relapses and partial remissions. Angina pectoris, coronary thrombosis or cerebral vascular accident, not immediately fatal, may bring the patient to a greatly reduced state of activity or a trying state of bed-ridden paralysis. Impairment of renal function is common but renal failure and uræmia account for less than 10 per cent. of deaths from essential hypertension. Intermittent claudication and gangrene are among the other terminal manifestations of the process.

With the onset of congestive failure or after the occurrence of a coronary thrombosis the blood pressure, especially the systolic

component, falls, and this is to be regarded as an ominous rather than an advantageous feature. Headaches, formerly severe, may now disappear and the last months or years of the patient's life, distressing enough, may be freed from this added distress.

There is little need in this terminal phase for any test of lability. The increased load has been in existence for many years and the secondary degenerative results are now firmly established.

In endeavouring to assess the prognosis in any given case of essential hypertension a number of factors fall to be considered. So-called malignant hypertension, though fortunately uncommon, occurs mainly in younger persons, particularly in the fourth and fifth decades. As its name implies it pursues a rapid course, usually ending fatally within two years. In people of this age it is therefore unwise to offer a prognosis without observing the patient's progress over at least a few weeks. A rapid increase in the hypertension, the development of papilloedema and retinal haemorrhages, and the finding of evidence of gross and advancing impairment of renal function will indicate a rapid termination. The majority of patients follow a relatively slow and benign course through the stages I have outlined and it may be five, ten, or twenty years from the discovery of hypertension in the first or second phases before the final breakdown. Essential hypertension developing in women at the menopause is often well tolerated for ten to twenty years, while if it is detected first in the age period 60-70, with no gross signs of cardiovascular damage, it may not shorten life. In women the prognosis is about twice as good as in men.

However, in general, the expectation of life of anyone suffering from essential hypertension is materially less than in comparable non-hypertensive subjects. Mortality is lowest when the systolic blood pressure is in the range 90-110 mm. (tuberculosis excluded), somewhat higher in the range 110-130 mm., and it then rises steeply with further elevations.

Patients whose blood pressures are very labile, in whom rest and sedation or the amytal test show a marked fall to normal or nearly normal levels, have a much better outlook than persons with elevated pressures which are incapable of much reduction by these measures even though the latters' figures during active ambulant existence may actually be lower. For instance, a patient whose blood pressure under ambulant conditions is 230/120 mm. but falls to 145/90 when tested, may live five to ten years longer than another with an ambulant pressure of 200/110 mm. which falls only to 180/105.

HIGH BLOOD PRESSURE *

By A. T. BARCLAY DICKSON, *O.B.E.*, M.B., Ch.B.

WE all know the patient with essential hypertension about whom Dr Hamilton has just been speaking, and we all know that this is one of those conditions of which we do not know the cause.

Such a patient is condemned to hypertension before he is born, but it is not sufficient to say that heredity is the main factor of causation. It is true that his father and grandfather before him had hypertension, but there must be some factor deeper than heredity which is the true cause.

It is not impossible that such a factor may be found in an inherent weakness of the metabolic functions, a breakdown in the proper katabolism of food, or in the ductless gland chain, or in both. The fact that the patient with essential hypertension is often greatly over-weight, rather points in this direction, as does modern treatment.

Whatever the cause, be it metabolic or be it endocrine, there are two things of supreme importance.

1. *The diagnosis of hypertension and above all the early diagnosis.* Hypertensives are of three types, two of them obvious to the eye and the third not so obvious. (*a*) The first type is tall, big-boned, muscular ; a strong man in his youth, but tending to become flabby and to put on weight when he gets to his forties. (*b*) The second, and certainly the most obvious and typical of all, is of middle height, has a high colour, red in youth and cyanotic in later life, a bull-neck and has also a tendency to become fat after middle life. He is, in fact, the typical plethoric individual. (*c*) The third is not in the least typical, and it will not occur to the examiner that he is hypertensive until he is taking the blood pressure. This patient is not big, he has not a high colour, he has not a bull-neck. On the contrary even beyond middle age he remains much the same weight as he was when in his twenties. He is slim built, and active both mentally and physically. He enjoys good health and apart from accident may never have been seriously ill in his life. On closer examination, however, it will be found that he is introspective, may have the so-called " inferiority complex " in greater or lesser degree, and is prone to worry and to be over-conscientious. He has imagination and is acutely aware of outside influences, both people and things. In other words, he has an over-active sympathetic nervous system ; and in this may be found possibly one of the root causes of hypertension.

* Read at a meeting of the Edinburgh Medico-Chirurgical Society on 16th January 1946.

2. *The Treatment.*—This largely means the instruction of the patient on how he should conduct his life. One thing that should be remembered is that the public at large is acutely conscious of " blood pressure." It is astonishing how many people have had relatives who have " blood pressure," or who have died of a " stroke," and therefore it is a common thing for a patient to approach his doctor with a ready-made diagnosis of " blood pressure," and as often as not the patient is right. It is therefore not sufficient simply to tell the patient lightly that he has a " touch of high blood pressure " for he is not in the least comforted by the information.

The psychic element in all three types of hypertension must be realised and the patient approached first from that angle.

Next and most difficult of all, the patient must be told that he must not over-exert himself or indulge in violent forms of exercise : he must avoid emotion and anxiety and must lead a quiet life, a life of ordered routine.

How can he do this ? He has a wife and family to provide for : jobs are not so easy to get and what he has he must hold, or see his family suffer, no matter how hard his work may be. He must just continue to heave those packing cases about, or wield a sledge-hammer, or help to put ton-weight rails in position. Even the business man is never free from anxiety, and the housewife must continue to keep her house in order and scrub and scour and cook from morning until night.

Diet is of the greatest importance, but again in these days of rationing is difficult to order. " Light diet " is the ideal with avoidance of fats and fries, pastries and pies and anything which is difficult to digest. In non-rationing times to be included among these things which are forbidden should be excessive carbohydrates owing to their tendency to increase obesity. The basic diet should be milk, eggs, vegetables and fruit, wholemeal bread and fish, steamed or grilled. Most important of all, however, the patient's food must not be cut down drastically to starvation level. More harm will be done by starving the patient than by over-feeding him.

As regards drugs there are very few that are of any use. In the past I have tried many remedies based on the metabolic and endocrine theories but never with more than temporary success, and now I believe that there are only two that are in the least effective, namely, ammonium bromide, gr. 15, and aromatic spirit of ammonia, min. 15. These two drugs act, I believe, in that they help to control the psychological element and induce healthy sleep.

One other point is of importance. For a reason which I shall give later, the patient should be instructed always to sleep on his side ; never on any account on his back.

A word of warning may be spoken here. Not every patient who is overweight has hypertension, and contrariwise a patient may have hypertension who is not overweight.

Recently a patient came to me with the ready-made diagnosis of " blood pressure " and he had all the appearance of the hypertensive and some of the symptoms. On examination, however, his pressure proved to be 138/74. I was so surprised that I took the pressure twice to make certain. On the other hand, a woman in her sixties, slim built, active and mentally alert complained to me that she had a tightness across her chest in climbing a stair or going up a slight hill. Examination of her retinal arteries showed the typical silver-lined arteries, and a blood pressure of 210/120. Both these patients are doing well at the moment on entirely different lines of treatment.

The next most common type of hypertension seen in general practice is the woman in the throes of the menopause. Not every menopausal patient has hypertension, but many of them do. It is true to say in fact that more women have some degree of hypertension at this time than have not. This patient again is typical. She complains of " flushings," headache, irritability, " nervousness," sleeplessness. There is little to be made out on physical examination beyond a degree of overweight and more or less hypertension. Sometimes the rise in blood pressure is so slight as to come within the bounds of the upper reaches of normality, but nevertheless it is usually there.

Treatment is well known. The administration of some form of œstrin in sufficient dose brings about an immediate response. All symptoms improve rapidly and the patient can quickly lead a normal life. In addition, the ammonium bromide—spirit ammon. aromat. mixture—mentioned already quickly controls the psychological element and induces sleep. As regards the hypertension the result is not so certain, but the general tendency is for the pressure to fall somewhat as the patient's general condition improves.

The third type of patient, the chronic nephritic, is seen much less frequently. In appearance he may be thin and wizened and rather miserable. The hypertension too is of a different type in that the diastolic pressure is relatively much higher, an important point in the differential diagnosis. His ultimate fate is usually that of the essential hypertensive, that is, a cardiac failure manifested by fibrillation, a coronary thrombosis or a cerebral hæmorrhage or thrombosis.

The cause of hypertension in the chronic nephritic is most difficult to understand, for it is not the fact that there is a glomerulo-nephritis which leads *per se* to hypertension, but some other factor altogether. While a breakdown in metabolism may be a possible cause, I feel that true understanding of the chronic nephritic can only be reached if the initial disease is regarded not as one affecting the kidneys only, but is one affecting the whole cardiovascular system in addition and concurrently.

The treatment here is difficult, for the patient as a rule only consults the doctor when the condition is far advanced, and the blood pressure is somewhere in the region of 200/130. Probably a regime of light

diet, rest and bromides, and the treatment of symptoms as they arise, is the best answer.

Mention has already been made of instructing the hypertensive patient always to lie on one side or other and never on the back. While investigating another aspect of hypertension some years ago I became aware, quite by accident, that the side blood pressure was considerably lower than that on the back. I noticed this several times and as a result I took the blood pressures of thirty people at random, mostly in a non-pregnant ward in the old Simpson Memorial Hospital. The series included two males. Almost without exception there was a marked difference in the two pressures, both systolic and diastolic, the average systolic difference being 10·9 mm. and the average diastolic 12·2 mm. The maximum systolic difference was 34 mm. and diastolic 30 mm. The result of this investigation was read at a meeting of the Obstetrical Society on 14th February 1934 and was published in this *Journal*.

Mention is made of this because so little is really known of hypertension that the smallest bit of additional knowledge is an asset and may lead to something else. I should be glad if those of you who are interested were to take this up and either prove or disprove my findings. After all, a series of thirty cases is very little and does not really prove anything.

When one thinks of hypertension one almost invariably thinks of essential hypertension, or chronic nephritic hypertension or some similar condition. But these diseases are all chronic. They have been present for years and the various systems are all deranged, and consequently any investigation into the root cause suffers under severe initial handicap. Surely the ideal patient for clinical and biochemical investigation is the young one with a young and elastic cardiovascular system and comparatively undamaged liver and kidneys. The difficulty is to find such a patient.

For a long time I have been interested in a particular aspect of hypertension, namely, that met with in pre-eclamptic toxæmia. For purposes of argument I would state that the essential cause of hypertension is the same, whatever the subsidiary and exciting causes may be and whatever the later clinical manifestations. In pre-eclamptic toxæmia you have not only a young or comparatively young patient but also a hypertension which is acute and early. Here you have undamaged liver and a cardiovascular system without arteriosclerosis, and here, therefore, is the ideal field for investigation.

In the limited time it is impossible to discuss this disease thoroughly ; suffice it to say that I have read American, Austrian and British articles and journals, and works on biochemistry, and have treated pre-eclamptic patients with some success along lines which I shall try to state briefly.

First the theory of ætiology. It is laid down as an hypothesis that pre-eclamptic toxæmia of pregnancy is caused by a breakdown

in maternal protein metabolism. It must be remembered that this toxæmia comes on at a time when the fœtus suddenly begins to grow at a relatively tremendous speed, and in order to cope with this rapid growth the woman's metabolism must increase in rate correspondingly. The woman who can adapt herself to this increase goes through pregnancy without incident, but if she is unable to adapt herself disaster follows. The theory then is that protein metabolism breaks down and intermediate products are released into the general circulation which are harmful and cause among other things a greater or lesser hypertension.

In the gastro-intestinal tract proteins reach their penultimate stage of digestion, and as amino-acids are taken to the liver by way of the portal system. In the liver deamination takes place and the resulting bodies are partly excreted and partly used in the building up of tissue. If the liver fails in this process of deamination, incompletely katabolised amino-acids are set free in the general circulation. Among these by-products are the guanidine group of compounds and these have been proved to exert a marked pressor influence. It has also been shown that there is an absolute calcium deficiency in pre-eclamptic toxæmia, and that calcium is an antagonist of certain of the by-products of amino-acids.

The picture then is that of a patient with hypertension caused by pressor substances which are the products of incompletely oxidised amino-acids.

What is the remedy ? The answer is ultra-violet light. The rays from 3900 to 2900 A° units, i.e. the long rays, penetrate to the deep layers of the dermis where there is a rich blood supply, and where they can exert their influence. Ultra-violet light is a very strong oxidising agent : it has been shown that deamination is the result of oxidation ; ultra-violet light will therefore complete the process in which the liver has failed.

As regard calcium metabolism, it is a fact that the ergosterol stored and manufactured in the dermis is changed to vitamin D when a patient is irradiated with ultra-violet light ; also that the utilisation of calcium by the body depends in great part on the presence of free *available* vitamin D. Irradiation, then, theoretically should raise the abnormally low blood calcium of pre-eclamptic toxæmia, and should make available an increased supply of calcium for combating toxins.

This then is the theory. Treatment was carried out on a number of patients (1) by a diet similar to the one detailed already, and (2) by irradiation with a mercury vapour lamp, and was attended by some success. As has been said it is impossible to go into full details, but sufficient of the theory and of the practical results was published in the *Journal* in 1935.

The main point is that in pre-eclampsia there is the ideal field for the investigation of hypertension if it is granted that hypertension, whatever courses it may follow, has always the same root cause.

DISCUSSION

Dr Miller referred to hypertension of different forms encountered during pregnancy. Whereas pre-eclamptic toxæmia had formerly been regarded as due to a hypothetical toxin of unknown nature and origin, the view now commonly held was that it was closely related to a generalised peripheral arteriolar spasm. The vascular disturbance was so closely similar to that associated with essential hypertension that many observers, notably Fishberg, claimed that they were identical. There seemed to be, however, adequate grounds for continuing to regard eclamptic toxæmia as a specific entity peculiar to pregnancy. On the other hand it was important to remember that hypertension was the earliest and most constant symptom, that it was the last to disappear, and that where after-effects persisted these were cardio-vascular rather than renal in character.

Dr Miller referred to the early diagnosis of the potential or actual pre-eclamptic, to the essentially progressive character of the disturbance, and to the difficulty or impossibility of preventing its development, or even substantially modifying its course. He emphasised the importance of rest, both mental and physical, as the most important item of treatment. He mentioned the important work of Page and Grollman on the extraction from the kidney of a vaso-depressant substance which was antagonistic to the pressor principle. The clinical employment of this substance has been claimed to give results which are highly encouraging, and the hope might be entertained that the beneficial effects obtained in non-pregnant hypertension might also be achieved in the closely parallel hypertensive toxæmia of pregnancy.

Dr I. G. W. Hill referred to the importance of general management in cases of hypertension. It was necessary for the patient to adapt himself and his way of life to his pressure rather than to attempt to lower the pressure in the individual patient. The patient must learn to take life easily, but it was important that unduly severe restriction of diet and activity should not be imposed. There was little evidence that drastic restriction of protein ever lowered the pressure or prolonged life, and it was clear that many patients felt unwell on such a regime. Further, before recommending drastic changes in activity the patient's work and environment must be considered. Where restriction of activity meant that the patient had to give up his means of livelihood, it should always be weighed carefully whether problematical gain of a year or two of life would offset the economic hardship imposed on a patient and his dependants.

Dr Dickson had referred to weight reduction as an important part of treatment. Dr Hill endorsed this and said that in cases of angina pectoris, which was frequently associated with hypertension, weight reduction was frequently the most powerful therapeutic agent available.

With regard to sympathectomy for cases of hypertension, Dr Hill had had some experience of cases treated by this method some years ago when technique was perhaps less perfect than now, and the results at that time were certainly not very encouraging.

Finally, Dr Hill reminded the meeting that high blood pressure was not necessarily associated with marked shortening of life. He recalled a report published in America some years ago of three cases with pressures over 200 mms. who had survived some twenty years from the time of initial diagnosis. Hypertension, he said, was a common disease and a killing disease,

but there were a large number of old people leading active lives who have had hypertension for many years. He recalled the case of a man of 87 who had had a cerebral vascular accident five months ago and when seen had gross cardiac enlargement, auricular fibrillation with complete heart block, and a blood pressure of 220/130. This old man came for opinion because he wanted to return to work.

Dr J. G. McCrie brought up the question of climate in relation to blood pressure. He had formed the impression, which was confirmed by another medical specialist who made a practice of taking the blood pressure in practically every patient he examined, that the pressures of British troops in Algeria were distinctly lower than were found in corresponding age-groups at home. He presumed that this was a merely temporary phenomenon in persons not yet acclimatised to new conditions, but at the same time would like to enquire of Dr Hamilton whether there was in fact any difference in the incidence of hypertension, and hypertensive cardiac disease, in countries with warm and cold climates respectively, or in say, the Southern States of America as compared with the Northern.

Dr H. M. Traquair referred to the oculist's interest in blood pressure. Patients attend the oculist complaining of headache, dizziness, diplopia and other symptoms suggestive of hypertension. If the patient is under 50 he tests his eyes; if over 50 he feels his pulse.

Another point is the relationship of retinal hæmorrhage to high blood pressure. In cases of retinal hæmorrhage much depends on the state of the arteries. If these are not badly diseased, even though hæmorrhage is present, the prognosis is not too bad, but this depends on how sheltered a life the patient can lead. After the appearance of retinal hæmorrhage the average expectation of life has been estimated at about five years.

Dr Kerr and *Mr T. McW. Millar* also spoke.

Dr Hamilton, replying, referred to the fact that the discussion had turned largely on the important subject of treatment. Hypertension was a problem which many met and had little idea what to do about—for the simple reason that there was no single sovereign remedy.

He thought it inadvisable to restrict a patient's activity too much. The possibility of extending his expectation of life by a year or two was often not worth the price of enforced leisure, difficulty in earning a living, etc. The risks the patient ran were not so very much greater than if he stayed in bed all the time. Where there was cardiac failure, of course, effort must be restricted.

As regards diet, there was little evidence that white meat had any advantage over red meat. There were experimental results showing that restriction of the intake of protein was not only of no benefit but might be harmful by producing a negative nitrogen balance and tissue wasting.

Dr Hamilton considered that surgical methods of treatment were only a stop-gap. He quoted figures given by Professor Learmonth from his own experience of 100-125 cases of sympathectomy for hypertension. Only about 25 per cent. showed any significant permanent reduction in blood pressure, an experience which was certainly in keeping with results published from other clinics. About 75 per cent. of these patients obtained symptomatic improvement, which was often very striking and quite sufficient to have

warranted operation. It was not certain, however, that the experimental error has been excluded, since a reduction in the level of the blood pressure of hypertensive subjects might follow such abdominal operations as chole-cystectomy.

Dr Hamilton commented upon Dr McCrie's question as to lower levels of blood pressure being observed in people who have gone from this country to reside in warmer climates. This observation had been made many times, but he knew of no statistics on the difference in the general blood pressure levels between the North of the United States of America as compared with the South. Essential hypertension was a very uncommon disorder in West African natives, but the negroes of the Southern States of America, mostly descended from West African negroes, showed a high incidence of vascular diseases in general, and hypertensive disease in particular. Differences in climate or environment might be involved, and there were doubtless other factors, such as working conditions, nervous strain, etc.

Dr Dickson also confirmed Dr McCrie's findings that the blood pressure is lower in a warmer climate. In the regrading of officers in 1941 in the Middle East the pressures were taken and the systolic found to range from 125 to under 110—some even as low as 100.

In the East, in countries where beri-beri is endemic, women may not exhibit any signs of beri-beri, but when they become pregnant, and especially from the fifth or sixth month onwards they may and often do develop it. This is due to the fact that the vitamin B reserve is low and that the fœtus will always take as much as it requires of everything from the mother no matter whether she can spare it or not, and no matter whether or not she suffers in the process.

Meeting of Edinburgh Medico-Chirurgical Society held at the East Fortune Unit, Bangour Hospital Annexe, on 15th May 1946.

Dr H. M. Traquair, President, in the Chair.

Professor Cameron discussed four cases of Disseminated Tuberculosis, demonstrating by X-ray films and detailed histories the multiple lesions found in these patients.

(*a*) A. P., female, aged 20 years, was admitted to East Fortune in August 1942 with a tuberculous right knee which was arthrodesed. She then developed tuberculosis of the breast. In March 1943 tubercle bacilli were found in her urine and she complained of dysuria and urgency. In April 1943 a lesion of the 5th lumbar vertebral body was found. Tubercle bacilli were demonstrated in a right breast abscess in July 1943.

The left kidney was removed in January 1945 and at the time of demonstration, the knee arthrodesis was firm, the breast and spinal lesions appeared to be healed and she was free from urinary symptoms apart from three-hourly frequency. Two small superficial sinuses remained on the nephrectomy wound.

(It is interesting to note that, since the meeting, a gibbus has been noted in the lower dorsal area and X-ray examination has shown a destructive lesion of vertebral bodies D 7 and 8 with a fusiform abscess.)

(*b*) K. W., female, aged 21 years, was admitted to East Fortune in January 1943. There was a history of tuberculous peritonitis in 1936. On admission she had a destructive spinal lesion with loss of joint space between L 3 and 4. A huge left psoas abscess was present above and below the left inguinal ligament. There was clinical and X-ray evidence of bilateral fibrotic lung disease. Soon after admission pus was noted in her urine and tubercle bacilli were demonstrated. Excretion pyelograms showed in March 1943 a hydronephrosis of the left kidney with great dilatation of the ureter.

At the date of demonstration the spinal lesion appeared to be showing advanced healing. The lung disease also appeared well healed. She had symptomless pyuria but tubercle bacilli were not present in recent specimens.

(*c*) S. W., male, aged 23 years, was admitted to East Fortune in January 1943. He had a history of right-sided pleurisy with effusion in 1940. On admission he had a large left pleural effusion and there were signs of fibrotic disease of the right upper lobe. A dorsal gibbus was present and X-ray showed destructive disease of vertebral bodies D 10 and 11.

Pyuria was noted in February 1944. A large rib abscess developed in September 1944 and required incision in February 1945. A swelling developed in the right thigh in July 1945 and thick pus and caseous plugs were aspirated.

In November 1945 he complained of stiffness of the right knee. The condition of the knee-joint suggested a synovial tuberculosis.

In April 1946 an ischio-rectal abscess was found and required incision.

At the time of demonstration the spinal lesion appeared to be showing advanced healing, the rib and thigh abscesses had absorbed and lung disease seemed quiescent. His right knee was painful at times and X-ray suggested remaining synovial disease.

(*d*) The X-ray films were shown of S. S., male, aged 17 years, who had been admitted to East Fortune in 1942 with dense disease of the 3rd lumbar vertebra. Soon after admission tubercle bacilli were found in his urine and excretion pyelogram showed a stone in the right kidney and abnormal pictures of each kidney. He was treated on a posterior spinal shell for twenty-one months and thereafter was kept for eleven months on postural rest in bed. At the time of discharge all lesions appeared quiescent but pyelograms showed no excretion from the right kidney. This man has been seen since discharge and remains very well, being free from urinary symptoms.

Professor Cameron discussed the method of dissemination in these cases, mentioning the rather benign type of pulmonary lesion which is very frequently a feature. He stressed the importance of the symptomless pyuria which was often the first evidence of a renal lesion.

(*e*) Professor Cameron also showed a patient who had a history of LUNG TUBERCULOSIS of twelve years' duration. He had recently been readmitted with marked extension of pulmonary fibro-cavernous disease but also with an ulcer on the inner right side of the lower lip about the size of half-a-crown. There was ulceration of the epiglottis which was split and almost completely destroyed. Ulceration extended on to the left vocal process. Dr Ewart Martin, who had examined the man, expressed the opinion that the laryngeal condition had the appearance of a lupus rather than a tuberculous laryngitis secondary to lung disease.

(Biopsy has since confirmed this opinion.)

Dr Murray, Medical Superintendent of East Fortune Sanatorium, showed the following patients whose lesions or treatment were discussed :—

(*a*) Two young female adults suffering from TUBERCULOUS ABDOMINAL ABSCESS which had presumably arisen from caseous mesenteric glands and had tracked behind the peritoneum to the iliac fossa where multiple sinuses had formed. In neither case had any spinal or other bone lesion been proved. Both had evidence of intestinal fistula as the sinuses intermittently discharged thin fæcal matter.

(*b*) Two female adults with SPINAL TUBERCULOSIS who had had advanced paraplegia and who had been treated by costo-transversectomy and anterior decompression. In one case Mr Norman Dott found compression of the spinal theca by tuberculous granulation tissue and by backward dislocation of an intervertebral disc. The disc was removed and a large anterior abscess evacuated by suction. Very rapid improvement had resulted in her general and neurological condition.

In the other case Mr Alexander evacuated a large paravertebral abscess and found severe compression of the theca by a ridge of tuberculous granulation tissue with a sequestrum. These obstructions were removed but to obtain satisfactory decompression it was found necessary to remove the posterior half of a diseased vertebral body and the intervertebral discs limiting the segment of disease. In this case also improvement had been rapid and most satisfactory.

(*c*) A child in whom CARIES OF THE CERVICAL AND UPPER DORSAL VERTEBRÆ had been treated by extension, using ice-tongs calipers applied to the skull and about 3 lb. traction obtained by rubber bands. Rapid improvement had resulted with almost complete disappearance of the signs of spinal cord compression which had previously been present.

(*d*) X-ray films of a woman who had a history of removal of a breast sixteen years before for scirrhous carcinoma and who had been admitted to East Fortune in December 1945 as a case of tuberculosis of the spine. The X-ray appearances had been considered to be more suggestive of a malignant deposit although there was a shadow very like that of a tuberculous spinal abscess. Since admission she had developed typical secondary malignant deposits in the pelvis and right femur with pathological fracture of the femur.

The unusually late development of secondary carcinoma and the difficulty of differential diagnosis of the spinal condition were discussed.

(At a subsequent post-mortem the paravertebral shadow which had been noted was found to be due to infiltration of the head of an adjoining rib.)

An interesting discussion took place on several of the cases which had been demonstrated and on the various manifestations and types of tuberculosis. Professor Cameron answered several questions relating to the pathogenesis of the disease and the varied types of primary lesions.

BEFORE AND AFTER LAËNNEC *

By DOUGLAS GUTHRIE, M.D., F.R.C.S.

SOME time ago, when I rashly undertook to contribute to this Society a paper dealing with the history of tuberculosis, I greatly underestimated the magnitude and the difficulty of such a task.

Given the necessary time and perseverance, a fair knowledge of general medicine and an interest in past events, the writing of a History of Medicine presents no insuperable difficulty. The history of a special branch of medicine, however, demands a historian who is also a specialist. Of tuberculosis, quite a series of histories might be written, each varying in its aspect of the subject. The history of the disease, the views of pathologists and of clinicians, the rise and development of sanatorium treatment, the evolution of laws and regulations concerning tuberculosis could each fill a volume, so that it is not easy to select. Speaking personally, however, my ignorance has considerably narrowed the field from which selection is possible, and I can indicate only a few of the principal signposts which may perhaps guide those of you who feel drawn more deeply into the study of the past.

The main object of this paper is to direct attention to some classic works on tuberculosis which are still well worth reading, although generally regarded as " out of date." The latest view on any subject may be, or ought to be, the most enlightened view, but it is not necessarily the most correct view. Osler spoke truly when he said, " it is a dry age when the great men of the past are held in light esteem." Old work need not be obsolete work.

So far as I am aware, only two detailed histories of tuberculosis have appeared in recent years, both of American origin. They are *The Development of our Knowledge of Tuberculosis*, by Laurence Flick, 1925, and *The Story of Clinical Pulmonary Tuberculosis*, by Lawrason Brown, 1941. To those books I am largely indebted for the information which, not without some diffidence, I am about to place before you.

In the writing of history there is one inflexible rule ; one must preserve a definite time-sense or chronology, so that each fact may be recorded in its particular sequence.

One of the best methods of presenting the subject is to pick out one striking or sensational event—in general history, a conquest, an empire, a dynasty ; in medical history, a discovery, a great teacher, a school—and around this event to group all other minor or accessory events. In surgery, the dominant figure is Lister, and every history of surgery is an account of events before and after Lister.

What was the most definite landmark in the history of tuberculosis ?

* Read at a meeting of the Tuberculosis Society of Scotland held in Edinburgh on 10th May 1946.

Was it the discovery of the bacillus by Koch in 1882 ? Or was it the early attempt of Bodington, in 1840, to establish sanatorium treatment ?

LAËNNEC AND HIS ACHIEVEMENT

I wonder if you will agree with me when I suggest that a more significant event than any was the publication by Laënnec, in 1819, of his classic work on Auscultation—*Traité de l'Auscultation Médiate*. Laënnec accomplished much during his short life. To-day, he is remembered as the inventor of the stethoscope, but that was only the first step in his great achievement, the tool which enabled him, to explore a new field. His book is no mere description of the stetho-scope ; it describes what the stethoscope can do. It is one of the great medical classics.

René Théophile Hyacinthe Laënnec was born in 1781, at Quimper in Brittany, the son of a local lawyer. He had the misfortune to lose his mother when he was six years old, and as his father was a fickle and purposeless man, young Théophile, as he was called, was consigned, with his brother Michael, to the care of his uncle William a physician at Nantes. Seven years later, when his father married again, Michael returned to Quimper, but Théophile remained, as he was determined to become a doctor like his uncle. Indeed, Laënnec owed little to his father, and everything to his uncle. He studied in the Medical School of Nantes, and then in Paris. His health was feeble, he was often very poor, but he was fortunate in his teachers and fellow students. His chief friend was *Gaspard Bayle*, his senior by seven years, who exercised upon him that beneficial influence which so often passes from a senior student to a junior. Bayle himself is an important landmark in the history of tuberculosis. Before he died of tuberculosis at the age of 42, he had performed nine hundred post-mortem examinations in cases of that disease, many of which he had also investigated clinically. Almost certainly Bayle was a martyr to science. He corrected many errors ; he showed that early and advanced pulmonary tuberculosis were one disease and not a whole series of diseases, and he was the first to use the term " miliary " in describing small tuberculous lesions.

Let us return, however, to the student life of Laënnec. Another senior associate was Guillaume Dupuytren, who later won great fame as a surgeon ; a cynical and intolerant man, and it is not surprising that Laënnec and he did not always agree. Laënnec studied medicine at the Charité under Corvisart, of whom more will be said. Bichat was the brilliant teacher of morbid anatomy and when Bichat died of tuberculosis in 1802, at the age of 31, Laënnec began to lecture on the subject and it was then that he discovered the sub-deltoid bursa, and proved that hydatid cysts were caused by a parasite. At this early stage of his career he busied himself in the study of Greek, the better to understand Hippocrates, and his thesis for which he received his diploma in 1804 dealt with " The Hippocratic Doctrine in relation

to the Practice of Medicine." During the next few years Laënnec worked strenuously, writing papers on many subjects, conducting a rapidly increasing practice, and studying and teaching at the Necker Hospital to which he was appointed Physician. All his work was based upon observation and experiment. Like Sydenham, he held that the practice of medicine should consist in observation rather than speculation.

It was in September 1816 that he made his great discovery. While examining a stout young woman it suddenly occurred to him that just as the scratch of a pin at one end of a log of wood is audible to the ear placed against the other end, even so might the sounds within the thorax be conducted to the ear of the observer. Rolling a note book into a tight roll he applied one end to the patient's chest and put his ear to the other, when he was " surprised and gratified " at being able to hear the heart sounds with great clearness and distinction. For a time he continued to use rolls of paper. Then he constructed a wooden cylinder which answered very well and was known as the " cylinder," the " baton," the " pectoriloquer " and, eventually, the " stethoscope." Yet Laënnec was no mere inventor of an instrument, though that was a clever piece of work. His real service was to show what might be accomplished by the aid of this tool, and to this task he devoted the remaining years of his short life. All those strange, unfamiliar sounds within the chest—whistlings, murmurs, wheezings, bleatings and crackling—were all to be analysed and arranged, and this was Laënnec's great accomplishment. It is little short of miraculous that this wasted, hollow-cheeked little man, already in the grip of the disease he was so closely studying, should have been able within a few years, to produce a book in which are described and classified all the sounds heard by the stethoscope. The first edition is dated 1819. It is a pleasure to read, and is universally regarded as a medical classic. But it almost killed the author. He was obliged to leave Paris and naturally he returned to his beloved Brittany, where he had a house, Kerlouarnec (the place of foxes), facing the Bay of Douarnenez. There, his health improved and two years later, in 1821, he returned to Paris and literally threw himself into work. He knew that it might kill him, but what was the loss of one life, he argued, if others could be helped. And so, he lectured and practised and laboured hard at the second edition of his book. He was now Physician at the Charité, Professor at the College of France and with a wide reputation as physician and teacher. He often lectured in Latin, for the benefit of foreign students who knew that language better than French, and he preferred the term " rhonchus " to " râle," which meant death-rattle and might be so interpreted by patients. He married Madame Argon in 1824, but he was to enjoy only two years of happy married life. In May 1826 he was again obliged to retire to Brittany, and on the afternoon of 13th August of that year he removed the rings from his fingers, explaining to his wife that he

preferred that no one should have the trouble of doing this for him
Two hours later he died. The second edition of his book had been
published just as he left Paris for the last time. It was translated
into English by Sir John Forbes, a man of culture and a good linguist
who graduated at Edinburgh in 1807 and, after serving in the Navy
for some years, conducted a large practice at Chichester and eventually
became physician to Queen Victoria. There were four editions of
his translation of Laënnec's book, the last in 1834. A still better
translation, though abridged, was published, with a *Life of Laënnec*
by Sir Wm. Hale-White in 1923.

Mention has been made of Laënnec's teacher Corvisart, who was
then at the height of his fame, soon to become a Baron, and physician
to Napoleon. *Jean Nicholas Corvisart* was a great teacher, though
rather dictatorial in his methods. It was characteristic of him that
his M.D. thesis was entitled " The pleasures of the study of medicine
and the disagreeableness of its practice." He was a keen student
of physiognomy and a master in the art of diagnosis at a distance
now, perhaps fortunately, a lost art. Nevertheless he was more
thorough in his examination of patients. " These," he told his students
" these are your books and you will find them more difficult to read
than printed books." Corvisart was an authority on diseases of the
heart, but his chief claim to fame lies in the fact that he drew attention
to the neglected discovery of Auenbrugger, which must ever be linked
closely with that of Laënnec. *Leopold Auenbrugger* (Laënnec called
him Avenbrugger), was born in 1722, the son of an innkeeper of Graz
and it is said that his idea of percussion was derived from the practice
of ascertaining, by tapping, the level of the fluid in his father's wine
casks. He studied under Van Sweiten in Vienna, became a popular
court physician, and wrote an opera entitled " The Chimney Sweep."
His only contribution to medical literature was a little book of 95 pages
now extremely rare, which bore the long title, *A new invention for
the Diagnosis of obscure internal diseases of the chest by percussion
of the Thorax.* Written in Latin, it is usually named from the
first two words of the title, " Inventum Novum." In this classic of
medicine, Auenbrugger compares the normal percussion note to that
of a drum covered with woollen cloth. He suggests that percussion
should be carried out " with a linen glove on the hand to avoid the
disturbing sound of striking the bare skin." He confirmed his facts
by injecting water into the chests of cadavers, and he made use of
his method for seven years before publishing his book in 1761.
Nevertheless it attracted little notice until Corvisart translated it into
French twenty years later. The English version appeared in 1824,
when it was included by Forbes in his translation of Laënnec's work.
Laënnec had a high regard for Auenbrugger and he believed that
percussion and auscultation had each an important part to play in
diagnosis. Corvisart used the open hand in percussion, a sort of
slapping rather than tapping. The plessimeter, or pleximeter, a little

plate of metal or ivory placed on the chest, was a later refinement introduced by Piorry of Paris in 1826. *William Stokes* of Dublin, who did so much to popularise the new methods in his book on *The Diagnosis and Treatment of Diseases of the Chest*, 1837, and who was one of the first to recognise the importance of early diagnosis, percussed against his finger placed with its dorsal surface on the chest.

Another physician who popularised the methods and views of Laënnec in this country was his pupil who afterwards became *Sir James Clark* (not to be confused with Sir Andrew Clark), and to whom the second edition of Forbes' translation of Laënnec's book was dedicated. In his own treatise, published in 1835, Clark drew attention to the importance of early diagnosis, and he sounded a warning against the practice of sending tuberculous patients away on long sea voyages.

Josef Skoda, who was the first to lecture in German (instead of Latin) in the Vienna School, added much to physical diagnosis by assigning to each of the sounds its musical pitch. Thus were the great contributions of Laënnec and Auenbrugger gradually accepted and employed.

It is not my intention to attempt to give a complete account of the history of tuberculosis, but the central position of Laënnec will become more obvious if we glance at the state of affairs before and after his time.

BEFORE LAËNNEC

It appears probable that tuberculosis existed in pre-historic times and although of course there is no written evidence, we may read it in the pathological appearance of Egyptian mummies, 1000 B.C., and in the votive offerings of Greek temples of Aesculapius of about the same date. One of the earliest written records, as we should expect, appears in the work of the Hippocratic School. There are a number of references in the Aphorisms to phthisis, although other wasting diseases may have been included under this category. "Phthisis was most common between the ages of 18 and 35; it was worse during autumn; diarrhœa was a mortal symptom." "In persons who cough up frothy blood, the discharge of it comes from the lungs." "Such persons as become humpbacked from asthma or cough before puberty soon die."

For the first clear description of pulmonary tuberculosis one must pass to the works of *Aretaeus*, who lived at Alexandria in the second century A.D. He distinguished between phthisis and empyema, thus: "If an ulcer form in the lungs from abscess, from cough, or from haemoptysis, the disease is phthisis. If matter form in the chest or side it is called empyema." Aretaeus goes on to describe phthisis: "All parts are slender and without flesh, no vestige of mammæ, joints prominent, eyes hollow and brilliant." "The persons most prone to the disease are the slender, those with prominent throats and whose scapulæ protrude like wings, who are pale and have narrow chests." Aretaeus classified disease as acute cases (including

hæmoptysis) and chronic (including phthisis). The relationship between them was as yet unknown, and even Laënnec focused his study upon the later stages of the disease. Aretaeus, however, was one of the first to recognise the benefit of living on or close to the sea, and he laid stress on the value of milk as a food. " If the patient live on the sea," he wrote, " it will be beneficial, as sea water is dessicant to the ulcers." It was not until 1796 that John Coakley Lettsom, the well-known Quaker physician, founded the Royal Sea Bathing Hospital at Margate for tuberculous children. After Aretaeus little advance was made in tuberculosis until the seventeenth century. Brief mention may be made of the use of the Royal touch for " King's Evil " swellings, tuberculosis of bones and joints and lymph nodes. The Royal touch had a long history, reaching its zenith in England in the reign of Charles II, who " touched " 4000 persons a year and attained a grand total of over 90,000. Richard Wiseman, the Father of English Surgery, condoned the practice, though he added that a surgeon might cure when the King was not available.

It was about this time that the study of morbid anatomy began, and that an effort was made to correlate the clinical with the post-mortem findings. The great work of *Morgagni* of Padua on the subject did not appear until 1761. It was *On the Seats and Causes of Diseases*, and described 700 cases. Morgagni located disease in the organs ; Bichat, in the tissues ; Virchow, in the cells. Nevertheless, long before Morgagni's day, the method of investigation had been adopted.

Franciscus Sylvius (1614-72), one of the first to teach clinically in the Medical School of Leyden, suggested that there were lymph nodes in the lung which might be attacked by scrofula, in the same manner as other lymph nodes. Not every disease with emaciation was to be called phthisis. Sylvius suggested that " tabes " should signify emaciation ; phthisis, an ulcer of the lung. But the next important contribution to the pathology of tuberculosis at this time was made by *Richard Morton*, whose *Phthisiologia* appeared in 1689. Morton, like Sylvius, thought that the lungs were " full of innumerable little glands." " No wonder," he writes, " that those who have King's Evil also have tubercles in their lungs." Morton described sixteen varieties of pulmonary tuberculosis and recognised the tubercle, which he distinguished from ulceration and regarded as the primary lesion. Among the causes of tuberculosis, besides " imprudent diet, over-study, thick smoky air, and troublesome passions," he mentioned " excessive salivation and spitting, which withdraws the nutritious juices from the body." One of his astute observations was that it was " surprising that anyone past his youth could die without a touch of consumption." That he recognised natural cure is evident from his remark that " sometimes the tubercles go off of their own accord." This is remarkable when we remember that tuberculosis was regarded as incurable in his day. He hastens

to add that "every consumption, though cured, is apt to return."
Another observation was that "Chalky stones, bred in the lungs, are
wont to tear the tender parts and cause bleeding." He also alleged
that "he who coughs lives long" and he explained this by stating
that such persons usually take good care of themselves. Poor Morton,
like his father before him and his son after him, died of tuberculosis.
Morton's detailed account of tuberculosis was a remarkable achieve-
ment, but it was too detailed. In all fields of knowledge, advance
is not just a steady progress. A subject becomes more and more
detailed and complicated and specialised, until it reaches a bewildering
complexity. Then some genius arrives on the scene and simplifies
it all at a single stroke.

So it happened that in the following century there lived yet another
medical victim of the disease, *William Stark* of Birmingham who,
during his short life of twenty-nine years, showed that the numerous
varieties decribed by Morton were simply various stages of the same
disease. His demonstration of the unity of tuberculosis was a great
advance. Meanwhile, the infectious nature of the malady was an
accepted fact. *Fracastorius*, one of the great medical figures of the
Renaissance, not only gave its name to syphilis, but wrote the first
book on epidemiology, *De Contagione*, 1546, in which he stated that
many diseases, including phthisis, were caused by "minute seeds,
or seminaria, which multiply rapidly," and which spread infection
by contact or even at a distance, through the air. Of course no one
had seen them, but the idea took root, and we find *Sydenham*, one
of the greatest of all physicians, writing that "certain diseases are
caused by particles in the atmosphere."

There was no lack of material for those early investigators. *John
Locke*, the philosopher and physician, the friend of Sydenham
wrote an essay on Tussis (Cough) in 1685 in which he said that
20 per cent. of all deaths in London were due to phthisis. Locke
referred to the benefit accruing from horseback exercise, but he failed
to recognise that the improvement was due to the open air rather than
the exercise. Many more names might be mentioned, but perhaps
enough has been said to illustrate the state of knowledge before the
time of Laënnec. Laënnec did not arrive on the scene unheralded.
That genius of the seventeenth century, Robert Hooke, a pioneer of
microscopy and a founder of the Royal Society, wrote "who knows
but that it may be possible to discover the works going on in man's
body by the sounds they make, as in a watch."

After Laënnec

Although Laënnec added greatly to the methods of diagnosis,
the death rate remained high. No cure had been discovered. The
first to recognise the importance of early diagnosis was another
physician of Paris, *Pierre C. A. Louis*, whose results were based
upon the careful statistical analysis of 2000 cases. Indeed, his second

great service was to show that exact figures are more valuable than vague impressions, and it is interesting to note that this statistical method is again becoming important in medicine. Louis' work, published in 1839, drew attention to the early signs of pulmonary tuberculosis, and to the fact that the apex of the lung was usually involved. Louis was a popular teacher and a good clinician. He always began by asking two questions. First, " How long have you been ill ? " and then, " Before that, were you perfectly well ? " and, having thus fixed the time of onset, his examination proceeded. Many American students attended his clinic, including Oliver Wendell Holmes, who learned three things from him—" not to accept authority when he could have facts, not to guess when he could know, and not to think that a man must take physic because he is sick."

Meanwhile another Morton, *George Morton*, in America, who had been a pupil of Laënnec, had written his *Illustrations of Pulmonary Consumption* (1834) and had noted the signs of incipient tuberculosis. Another excellent description of early tuberculosis was written in 1846 by *Henry Bowditch* of Boston, a pupil of Louis. He called it *The Young Stethoscopist or the Student's Guide of Auscultation.* Lawrason Brown considered it the best account of early pulmonary tuberculosis that has ever been written. A later American authority, who has been called " The American Laënnec," was *Austin Flint* of New York, well known for his work on cardiac disease and on tuberculosis. He analysed 670 cases of tuberculosis in a book (1875) which is still in use.

I shall not attempt in this paper to deal with the work of *Jean Antoine Villemin*, the French army surgeon who, in 1865 (the year of Lister's discovery), proved that tuberculosis could be produced in rabbits by inoculation. Nor shall I do more than mention the immense services of *Robert Koch,* and the medical revolution which followed his discovery of the tubercle bacillus in 1882.

In the short time now at my disposal I should like to refer to the early days of open-air treatment, as the facts are perhaps less familiar, though doubtless well known to the present audience. Recognition of the disease in its early stages naturally led investigators to search for a cure. No longer was tuberculosis to be regarded as a hopeless and incurable disease. And as so often happens in the history of medicine, the first step was taken by an obscure general practitioner. Born in the last year of the eighteenth century, *George Bodington* was in practice at Erdington, near Birmingham, when he wrote his famous *Essay on the Treatment and Cure of Pulmonary Consumption*, 1840. He condemned the prevailing practice of " shutting patients up in a close room and forcing them to breathe over and over again the same foul air." " To live in and breathe freely the open air was the one essential remedy." The cooler the air was the better. Therefore he advised early rising so that the " cool pure morning air might have its sedative effect upon the interior surface of the lungs." He also advised

abundant food (nourishing diet and wines) but he did not recognise the value of rest, and he perpetuated the tradition of exercise on horseback and of long walks. Nor did he realise the need for sleeping in the open air. His attention was more closely drawn to the problem when he observed that few of the awl grinders of Sheffield lived beyond the age of thirty. The town hospital, in his opinion, was the " most unfit place imaginable " for cases of tuberculosis. There should be special hospitals in country surroundings, with " provision for horse and carriage exercise " and " gardening and farming for convalescents." After treatment the patient should not return to town but should continue out-door work. " There ought to be a class of practitioners who would pursue this practice as a special branch and receive patients into their own houses in the country."

Bodington gives details of six cases, treated with good results. In 1843, he transferred to Sutton Coalfield, near Lichfield, and continued his plan of treatment. Nevertheless he met with scant encouragement and was obliged to turn his establishment into a mental hospital.

Another pioneer, who apparently was unaware of Bodington's work, was *Henry MacCormac* of Belfast, who graduated M.D. at Edinburgh in 1824. Bodington became discouraged and gave up his fight for fresh air, but MacCormac preached his gospel for years, in season and out of season and refused to accept defeat. He lived at a time when night air was considered a deadly poison and the atmosphere of every sickroom was foul and stuffy. On more than one occasion he poked his umbrella through the window pane of his patient's bedroom, and once he was obliged to defend such a practice in the police court. " If I had a Stentor's voice and an angel's pen," he wrote, " I should employ them to enlarge my views." " There can be no immunity from phthisis until medical practice and popular conviction concur as to the indispensableness of pure fresh untainted air, at all hours, at all times and in all places." When his paper on " The Preventibility of Consumption " at the Royal Medical and Chirurgical Society of London in 1861 was read in his absence by the Secretary, it was received so adversely that the meeting declined to pass a vote of thanks. Nevertheless his treatise on *Consumption* was published in 1855, and his enlightened views were welcomed on the Continent where *Hermann Brehmer* held similar views amid the jeers of his colleagues and eventually opened the first sanatorium at Goerbersdorf in Silesia in 1859. One of Brehmer's patients, Peter Dettweiler, built his own sanatorium at Falkenstein in 1876 and he was probably the first to recognise the value of rest and the possible danger of exercise. It is not known whether either of those German physicians was aware of the similar views of Bodington and MacCormac.

In America, the pioneer of open-air treatment was *Edward Livingstone Trudeau*, whose sanatorium for persons of moderate means began its work at Saranac Lake in 1884.

Trudeau, himself a tuberculous patient, laid stress upon the pre-tuberculous stage of the disease. He drew attention to the method of bringing out latent rāles by a cough at the end of expiration.

Here the story must end. I have left much unsaid : the progress of organisation and control and prevention ; the introduction of artificial pneumothorax ; the development of X-ray diagnosis ; and various other aspects of the great problem. It is fitting that the last slide should remind you of the greatest of Scottish phthisiologists, perhaps the greatest of all, *Sir Robert Philip*, whose teaching was an inspiration to some of us and whose gracious personality was so helpful to many a student and patient. His dispensary for tuberculosis was opened in Bank Street, Edinburgh, in 1887.

One could not hope, in a short paper, to tell the whole story of pulmonary tuberculosis. But in this mechanical age, with its attempts to produce a rule-of-thumb medicine based upon technical principles, it is salutary to remember the past and to honour the pioneers. Although I am no longer a clinician and although perhaps I have no right to express an opinion, I make bold to say that it will be a sad day when the stethoscope becomes an obsolete instrument, and when the classics of Morton and of Laënnec are no longer read. Especially Laënnec, for he is the central figure of the story, the Lister of tuberculosis, the most doughty knight who ever bore a lance against " the captain of the men of death."

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THE LABORATORY DIAGNOSIS OF INFLUENZA

A Summary of Current Methods

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METHODS for the laboratory diagnosis of influenza have been greatly improved of recent years, and a variety of techniques are now available. Attempts should be made both to isolate the virus from the respiratory tract, and to demonstrate a rise in specific antibody in the serum.

A. Isolation of Virus

Preparation of Inocula.—An attempt should be made to isolate the virus from patients, partly to establish the diagnosis of influenza, and partly so that the strain can be analysed antigenically. The patient is instructed to gargle about 10 c.c. of broth or saline ; saline can afterwards be mixed with 5 c.c. of broth. The material is then roughly clarified by paper filtration. Such " raw " washings can be inoculated intranasally in ferrets and other animals or in eggs (see below) ; or a Gradocol membrane (A.P.D. $0·8\,\mu$) filtrate can be prepared. Hoyle (1944) recommends filtration through sintered glass filters (maximum P.D. $1·5\,\mu$).

In fatal cases filtrates should be prepared from lung suspensions. Himmelweit (1943) recommends centrifuging 20 per cent. tissue suspensions at 3000 r.p.m. for thirty minutes, and filtering the supernatant through three superimposed Gradocol membranes arranged in descending order of size (A.P.D. $1·5$, $1·05$, and $0·7\,\mu$ respectively). Alternatively a Berkefeld filtrate can be used, preferably obtained after preliminary clarification (Parker *et al.*, 1946).

Certain workers have attempted to concentrate any virus that may be present in throat washings. Thus, washings can be treated with red cells to adsorb virus, and after eight to ten minutes Zephiran (1/20,000) is added to inhibit contaminants. After twenty-five minutes, the cells are spun down, and resuspended in 1 c.c. of saline, which is available for inoculation (U.S. Nav. Med. Lab., No. 1, 1946). Alternatively, the garglings are centrifuged for half an hour at 12,000 r.p.m. to throw down organisms ; human O cells are then added to the supernatant fluid to a final concentration of 1 per cent. ; finally, the red cells plus adsorbed virus are spun down and resuspended in 1 c.c. of saline, which is available for injection in eggs (U.S. Nav. Med. Lab., No. 1, 1946).

If it is not convenient to examine washings immediately obtained, they can be stored for several months, at $-76°$ C. (Francis *et al.*, 1937 ; Hirst, 1942 *b* ; Taylor and Parodi, 1942).

Inoculation of Ferrets and Hamsters.—Virus was originally isolated by the Hampstead and other workers by nasal instillation of ferrets, and this method should still be tried whenever possible. Ferrets should be inoculated with clarified garglings or Gradocol filtrates. In the presence of the virus, ferrets develop characteristic catarrhal signs and fever in forty-eight hours or so. It is usual to pass suspensions from turbinates or lungs three to five times before regarding a result as negative.

As emphasised by Andrewes, virus strains vary greatly in their infectivity for ferrets. Typical epidemic strains of virus A can usually be established without much difficulty, but strains recovered in inter-epidemic periods may be difficult to establish, even by " blind " passage (Burnet and Lush, 1940 ; Lennette *et al.*, 1941 ; Taylor and Dreguss, 1941 ; Andrewes, 1942 ; Andrewes and Glover, 1944). B strains seem to be difficult to adapt to ferrets (Eaton and Beck, 1941 ; Taylor *et al.*, 1942-3 ; Dudgeon *et al.*, 1946).

Hamsters can largely replace ferrets (Taylor, 1940 ; Lennette *et al.*, 1941 ; Taylor and Parodi, 1942 ; Taylor *et al.*, 1942-3 ; Eaton *et al.*, 1945).

Instead of killing ferrets or hamsters and passing their tissues, the animals may be bled two weeks after intranasal inoculation of washings, and their sera examined by any of the recognised methods for neutralising or complement-fixing antibodies (Magill, 1940 ; Hirst, 1942 *b*, 1945 ; Taylor and Parodi, 1942 ; Parodi, Pennimpede, and Vilches, 1944 ; Eaton *et al.*, 1945).

Inoculation of Mice.—As a general rule, it is not possible to pass influenza virus direct from man to mouse by nasal instillation of garglings (Burnet and Lush, 1940 ; Mulder, 1940 ; Taylor and Dreguss, 1941). Some workers, however, have achieved success (Sulkin, Smith, and Douglass, 1941 ; Sulkin, Bredeck, and Douglass, 1942). The ease of adaptation of ferret-passaged material to mice varies considerably, and virus of Andrewes' low grades may not infect mice at all. B strains are difficult to adapt to mice, but generally after a few ferret passages virus A strains can be passed fairly readily with the production of pneumonia. Japanese workers have claimed the isolation of strains from centrifuged washings in mice blockaded with India ink (Tsurumi, Ogasawara, and Fujil, 1941). When first attempting to pass strains to mice, it may be necessary to passage lung suspensions intranasally although the organs show no evidence of pneumonia—so-called " blind " passage.

Instead of attempting the isolation of virus by passing suspensions of mouse lungs, some of the animals inoculated intranasally can be bled after fourteen days and their sera tested for antibody ; the remainder of the batch can be tested for the development of resistance to the inoculation of a stock strain (Burnet and Foley, 1941).

Other Animals.—According to Weir (1944) cane and bush rats can also be used.

Inoculation of Eggs.—The fertile egg has been widely used in the isolation of influenza viruses from raw washings, filtrates, or washings treated with antiseptics or antibiotics (for details of the technique of inoculating eggs, see Beveridge and Burnet, 1946). In general, infection is indicated by the presence of chick cell agglutination with egg fluids, or by pathological changes in the embryo.

Eggs may be inoculated with filtrates in the yolk-sac (Beveridge, Burnet, and Williams, 1944) or on the chorio-allantoic membrane (Chapman and Hyde, 1940), but these routes are not much used.

Allantoic inoculation is more widely employed.

(*a*) Raw washings (0·2 c.c.) can be inoculated without any treatment; influenza virus will develop in a proportion of the eggs even if bacterial contaminants grow also (Thigpen and Crowley, 1943; Adams, Thigpen, and Rickard, 1944; Crowley, Thigpen, and Rickard, 1944; Rickard, Thigpen, and Crowley, 1944, 1945; Eaton *et al.*, 1945; Hirst, 1945; U.S. Nav. Med. Lab., No. 1, 1946).

(*b*) Such raw washings can be treated with penicillin (Hirst, 1945; Rose, Milloy, and O'Neill, 1945; Francis, Salk, and Brace, 1946), penicillin and sulphonamides (Burnet and Stone, 1945; Burnet, Stone and Anderson, 1946), or streptomycin (Lowell and Buckingham, 1946).

(*c*) Chemicals such as Emulsol, 1/4000 (Henle *et al.*, 1946), or Zephiran, 1/20,000 (U.S. Nav. Med. Lab., No. 1, 1942) can also be added to the raw washings, which are inoculated after fifteen to twenty minutes contact.

(*d*) Gradocol filtrates can be used.

After inoculation of any of the above materials, allantoic fluid is tested for virus by the chick cell agglutination technique; equal parts of allantoic fluid and 2 per cent. fowl cells are mixed on a white tile; the presence of agglutination in a short time indicates the presence of the virus. It should be realised that occasionally fluids containing organisms may give a " false positive " agglutination of chick cells; this reaction is inhibited by normal serum (Florman, 1946). If the result is negative, the fluid should be passed serially through three to five more eggs.

Amniotic inoculation is probably more sensitive than allantoic inoculation, and as shown by Burnet (1940 *a, b*) is an excellent, probably the best, method of isolating virus.

(*a*) One may inoculate 0·1 c.c. of raw washings treated with penicillin (Hirst, 1945; Francis, Salk, and Brace, 1946), or penicillin and sulphonamides (Burnet and Stone, 1945; Burnet, Stone, and Anderson, 1946; Dudgeon *et al.*, 1946). This latter is perhaps the most satisfactory of any method of laboratory diagnosis in influenza. Burnet and Stone (1945) recommend that the patient gargles 10 c.c. of saline for one minute; 5 c.c. of broth are then added, and enough penicillin to make a final concentration of about 100 units per c.c. This material is filtered through sterile filter paper to remove gross

particles. Amniotic inoculation with 0·1 c.c. of washings is then performed in a thirteen-day embryo, 0·1 c.c. of 5 per cent. sodium sulphadiazine being first inoculated in the same cavity.

(b) Chemicals, as mentioned above, may be added.

(c) Most work has been carried out with Gradocol or similar bacteria-free filtrates (Burnet, and Foley, 1940, 1941 ; Rudd, 1941 ; Stuart-Harris, 1941 ; Burnet et al., 1942 ; Hirst, 1942 b, 1943, 1945 ; Burnet and Bull, 1943 ; Burnet, Beveridge, and Bull, 1944 ; Beveridge, Burnet, and Williams, 1944 ; Hoyle, 1944 ; Eaton et al., 1945 ; U.S. Nav. Med. Lab., No. 1, 1946).

The presence of infection is shown by chick cell agglutination given by the amniotic or allantoic fluid, and by characteristic microscopic appearances in the tracheal exudate and lungs. If the first passage proves negative, transfers should be continued with amniotic fluid, or ground-up lung or trachea (10 per cent. suspensions). Virus B is less easy to isolate than virus A.

It must be remembered that normal amniotic fluid after about the thirteenth day causes agglutination of various red cells, but not of chick cells ; the titre, however, is not above 32 (Commission on Acute Respiratory Diseases, 1946).

Inoculation of Tissue Cultures.—It has been claimed that virus can be isolated by inoculation of tissue cultures.

B. SEROLOGICAL TESTS

The serum of most " normal " adults contains a measurable quantity of influenzal antibody, due to previous infection, detectable by complement-fixation, neutralisation tests in mice or eggs, or more, usually by the inhibition of chick red cell agglutination (CCA-inhibition).

Antibody is therefore present in the serum in the first few days of an attack, but in convalescence the titre detected by any of the above methods rises. While a reproducible two-fold rise may be accepted as diagnostic, the increase may be four- to sixteen-fold or even more. In general, the lower the initial titre the higher the convalescent titre ; *vice versa*, rises may not be detected in those whose initial titres are already high. Serological tests are carried out on a serum obtained in the first day or two of illness (acute phase sample), and on a convalescent phase sample obtained after ten to fourteen days. Both tests should be carried out at the same time by an identical technique.

It is important to remember that in a small percentage of cases, especially those with high initial titres, no antibody increase may be detected in convalescence. Not uncommonly, an antibody increase occurs in the absence of symptoms, due to subclinical infection.

It will not here be possible to detail the techniques to be followed in serological investigations, but certain easily accessible papers provide the necessary information : virus-neutralisation tests in mice

(Horsfall, 1939; Burnet and Clarke, 1942); virus-neutralisation tests in the allantoic cavity (Hirst, 1942 *a* ; Burnet, 1943 ; Bull and Burnet, 1943 ; Beveridge and Williams, 1944); virus-neutralisation by the CCA-inhibition technique (Hirst, 1942 *c* ; Hirst and Pickels, 1942 ; Burnet *et al.*, 1945 ; U.S. Nav. Med. Lab., 1943 ; Miller and Stanley, 1944 ; Salk, 1944 ; Lauffer and Carnelly, 1945 ; Dudgeon *et al.*, 1946).

CONCLUSIONS

The most satisfactory method of attempting virus isolation is probably by the inoculation of washings in the amniotic cavity, using penicillin and sulphonamide to minimise the risk of infection with cultivable bacteria. The more tedious methods of animal inoculation take second place, but should be tried when possible. As a method of retrospective diagnosis, and in epidemiological surveys, serological investigation by the chick cell agglutination-inhibition technique is of the greatest value.

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A CASE OF CALCINOSIS UNIVERSALIS *

Dr Donald showed a case of CALCINOSIS UNIVERSALIS in a woman aged 60. Symptoms had first developed at the age of 51, with pain and swelling in the thumb and middle fingers of the right hand. The process spread to involve all the fingers of this hand, and a month or two later both feet became involved. Within six months the left hand became painful. With the onset of the swelling and the pain she noticed that her fingers tended to become bulbous, and her nails shorter and more brittle.

Two years later the tips of the fingers developed hard white nodules, and similar nodules also appeared on the right shin and on lateral aspect of both heels. During the next three years nodules came up on the front and sides of both thighs and both forearms.

For the past two years, marked evidence of Raynaud's phenomenon had been present in both hands. At the same time, the skin across her chest and forehead became glossy brown and exceedingly tight. These latter signs had now regressed to some extent, but the Raynaud's phenomenon had become worse, and the number of nodules had increased, so that any movement of the hands was now painful.

Although the nodules consisted of calcareous deposits, repeated investigations had failed to show any abnormality in the calcium metabolism of the patient ; and her blood calcium level, blood phosphatase concentration, and calcium balance had at all times been within normal limits.

Dr Donald demonstrated the wide-spread deposits of calcium in the patient, many of which were easily palpable ; the deformities of the fingers ; and the scleroderma which particularly affected the skin of the chest.

The X-ray findings were reviewed by Dr McWhirter. There was marked calcification of the right gluteal region, and also some calcification within the pelvis, possibly affecting the uterus. The hands were extensively involved all along the pulps of the fingers, especially in the left index finger, extending into the tendon sheaths, with marked atrophy of the terminal phalanges. Calcification of the feet was less striking, but there were large areas of it over the os calcis. Calcification lay in relation to joints and bursæ, and in the intermuscular planes.

Prof. McCance said that he had no doubt of the diagnosis in this case, but he thought that the age of the patient under review was a little unusual for calcinosis universalis. As regards its ætiology, did they think it was a disturbance of calcium metabolism at all ? He personally did not. He had been interested in the disease for about twelve years and he thought he could explain it better if he ran over it historically.

About 1934, Dr Sheldon of Wolverhampton had a very bad case of calcinosis in a man aged 22, with deep plaques in the fascial planes of the muscles. A big plaque on the hip was surrounded by fluid, as they occasionally were, and it was exactly like milk. Dr Sheldon sent some of this fluid for analysis, and they found it was a serous exudate, the milky appearance being due to colloidal particles of calcium phosphate. The ratio of calcium to phosphorus was the same as in bone, because of course, any deposit of calcium and phosphorus tended to approximate to that ratio. After the fluid had been removed, it accumulated again quite rapidly, but on this second occasion it was hardly milky at all, and they found that there was almost as much phosphorus in it as before, but very little calcium.

This made them think very deeply, and they could not help feeling that in all probability the accumulation of fluid was filled with inorganic phosphorus first, and that the calcium was a secondary deposit, because any fluid containing a large amount of inorganic phosphorus would inevitably have calcium precipitated with the deposit and would assume the milky appearance they got before. Why should there be such an enormous amount of inorganic phosphorus in a serous fluid accumulated in the body? The obvious explanation was that there was an abnormal amount of alkaline phosphatase in the tissues round the bursæ. Within the last eighteen months a new histological method of examining tissues for phosphatase had been developed. They had to be careful how the biopsies were taken, and what metals were used, and the glass in which the preparations were made had to be kept scrupulously clean. They had examined three cases of calcinosis by this method, and there was no doubt at all that the tissues round the plaques, wherever they might be, were packed with alkaline phosphatase. They had not yet been able to decide, however, to what extent this was the normal response to a foreign body, nor had they enough controls to be quite certain that no normal person's tissues contained phosphatase in similar quantities.

He thought that they must consider this to be a localised disease of the tissues, and not a generalised systemic disturbance. He thought that it was a very reasonable proposition that the deposit of calcium was secondary to an abnormal liberation of inorganic phosphate, which presumably was due to an abnormal development of phosphatase enzyme in the tissues. Why the phosphatase should develop he did not know. He had no explanation to offer, but, if that was the case, the discovery of B.A.L. and B.A.L. Intrav. did offer a possibility of therapy, because these compounds knocked out the phosphatase temporarily.

Prof. Dunlop said that the chest was rather typical of scleroderma two years ago, but it had changed in the interval.

Prof. McCance said that this particular manifestation and scleroderma often occurred together. He had not enough experience of scleroderma to say how closely the two conditions were associated.

Prof. Learmonth observed that in London he had seen some slides which showed that a very large amount of phosphatase was present in the neighbourhood of a healing wound. Could they not explain the large amount of phosphatase found locally in calcinosis as an effort to heal or deal with local deposits?

Prof. McCance replied that they had thought of that. Leucocytes were a great source of phosphatase but there were comparatively few round these deposits, unless they were infected.

Dr Wallace referred to a case of calcinosis in a young child which he had seen in Holland. The deposits very largely disappeared with massive doses of sodium citrate. The X-rays of this case were very striking.

Prof. McCance said that they knew these cases sometimes healed spontaneously. The new preparation, B.A.L. Intrav. was difficult to get, and it had scarcely reached the general therapy stage.

Prof. Dunlop asked if all cases of calcinosis showed the Raynaud phenomenon?

Prof. McCance said that he did not think they did ; not the children.

Prof. Dunlop thought it was fairly constant among the adults. The woman shown to-day had a fair degree of Raynaud's disease.

Prof. Learmonth said they were accustomed to see small deposits of

calcium in the tips of the fingers in Raynaud's disease, but nowhere else, and it was an individual variation. Not all cases of Raynaud's disease showed it, and it did not seem to be related to the severity of the attacks, but to the period over which they lasted. On the other hand, when they saw scleroderma in children, which they sometimes did, he agreed that if they waited long enough it might improve, but he did not think that he had seen calcium deposits in a child.

Discussing scleroderma, calcinosis and Raynaud's disease, Prof. Learmonth said that the underlying process could not be the same in all these conditions, and that it could not be due to a vascular defect in scleroderma, although formerly sympathectomy had been employed for this disease. Some sclerodermas were relentlessly progressive, especially in older people ; but if they saw scleroderma in a child it was wiser to wait for a period of years before they attempted surgery. Looking at the picture of calcinosis, it gave the impression of being the " little brother " of myositis ossificans. The latter had the same widespread distribution, but in muscles, and the process had gone a stage further.

He added that Prof. McCance's suggestions regarding the ætiology of calcinosis linked up with those people who got heterotopic deposits of bone in operation scars. Curiously enough, the most common operation was one in which the bladder was involved.

Prof. McCance inquired if that was not perhaps due to the connection between phosphatase and the healing tissue ?

Prof. Learmonth agreed. There must be some individual variation. It was not common to find heterotopic bone, but cases were frequent enough to excite curiosity. It might be that these people had some variation in their powers to produce phosphatase and in the effects of the phosphatase they produced.

Dr McWhirter pointed out that in some people who had had a hæmorrhage no calcification developed, while in other cases marked calcification occurred. Calcification in fibrous tissue was not uncommon. It did seem that calcinosis might be an exaggeration of the normal response.

Prof. McCance thought that it was very tempting to try and relate these deposits of calcium in people with calcinosis to sites of trauma, but it was not always possible. Deposits undoubtedly occurred where there was no likelihood of trauma.

Prof. Learmonth asked if it were possible with such a drug as sodium citrate, or with any drug, to reach calcium deposits at this stage ? Surely the vessels must be pretty well sealed off ?

Prof. Dunlop said that it was almost unbelievable that sodium citrate could have any effect, or that any drug could get near these deposits.

Prof. Learmonth thought that if a drug could be diffused locally by some method of administration they might get the calcium deposits away.

Prof. McCance said that he thought the only hope lay in the treatment of very early deposits of calcium. He would let them know what results they got when they finished their examination of tissue phosphatase in these conditions.

Dr Glazebrook, in concluding the discussion, said that therapy did not seem to be feasible in the case of the poor woman shown to-day, but Prof. McCance's views of the ætiology of the disease held out the hope that one day treatment would be effective if carried out in the early stages. They were grateful to Prof. McCance for coming to Edinburgh to see what he could do to help this patient.

NOTES

THE Annual Meeting of the College was held on Thursday, 5th December, when Dr D. M. Lyon was re-elected President. Drs **Royal College of Physicians of Edinburgh** W. D. D. Small, C.B.E., L. S. P. Davidson, J. D. S. Cameron, C.B.E., H. L. Wallace, I. G. W. Hill, C.B.E., and D. K. Henderson were elected to form the Council of the College for the ensuing year. Dr W. D. D. Small, C.B.E., was nominated Vice-President.

AT a meeting of the Royal College of Surgeons of Edinburgh, held on 20th December 1946, Mr James M. Graham, President, in the **Royal College of Surgeons of Edinburgh** Chair, the following who passed the requisite examinations were admitted Fellows :—Louis Weston Aldridge, M.B., CH.B. UNIV. BIRM. 1936 ; Donald Rose Beaton, M.B., CH.B. UNIV. EDIN. 1934, M.R.C.O.G. 1941 ; Eric Norman Brockway, M.R.C.S. ENG., L.R.C.P. LOND. 1932, M.B., B.S. LOND. 1934 ; James Tulloch Brown, M.B., CH.B. UNIV. GLASG. 1938 ; John Edward Buck, M.B., CH.B. UNIV. EDIN. 1937 ; David Robinson Cairns, M.B., B.CH., B.A.O. QUEEN'S UNIV. BELFAST 1929, M.R.C.O.G. 1939 ; Archibald Matthew Gilchrist, M.B., CH.B. UNIV. GLASG. 1937 ; William Girdwood, M.B., CH.B. UNIV. WITWATERSRAND 1937 ; Subodh Chandra Gupta, M.B. UNIV. CALC. 1927 ; Albert Edward Khan, M.B., B.S. UNIV. SYDNEY 1936 ; Louis Kobrinsky, M.D. UNIV. MANITOBA 1933 ; Michael Maurice Kriseman, M.B., CH.B. UNIV. WITWATERSRAND 1935 ; Vincent Paul McAllister, M.B., B.CH., B.A.O. UNIV. COLLEGE, DUBLIN 1939 ; Hugh Cameron McLaren, M.B., CH.B. UNIV. GLASG. 1936, F.R.F.P. AND S. GLASG. 1938 ; Maxwell Alfred Margo, M.R.C.S. ENG., L.R.C.P. LOND. 1937 ; Elizabeth Theodora Mess, M.B., B.S. UNIV. LOND. 1930 ; Robert Frederick Moody, M.B., CH.B. UNIV. NEW ZEAL. 1938 ; Henry Dendy Moore, M.B., B.S. UNIV. SYDNEY 1936 ; Joseph Chappell Morris, M.B., CH.B. UNIV. MANCH. 1933 ; John Douglas Muir, M.B., CH.B. UNIV. L'POOL 1939 ; Keith Gardner Pascall, M.B., B.S. UNIV. LOND. 1938 ; William Ian Paterson, M.B., CH.B. UNIV. EDIN. 1938 ; Herbert Edwin Pearse, M.B., CH.B. UNIV. BRISTOL 1933, M.D. 1936 ; Richard Percy-Lancaster, M.B., CH.B. UNIV. EDIN. 1940 ; Charles Joseph Trajanus Pinto, M.B., B.S. UNIV. BOMB. 1940 ; Bernard Polonsky, M.B., CH.B. UNIV. L'POOL 1937 ; Cecil Ian Raeburn, M.B., CH.B. UNIV. ST ANDREWS 1937 ; Gavin James Ralston, M.B., CH.B. UNIV. EDIN. 1939 ; William Reid, M.B., CH.B. UNIV. GLASG. 1933 ; Archibald St Clair Robertson, M.B., CH.B. UNIV. EDIN. 1936 ; Thomas Berkley Russell, M.B., CH.B. UNIV. EDIN. 1940 ; Arthur William Booth Strahan, M.B., CH.B. UNIV. EDIN. 1935 ; Eric Joseph Tamblyn, M.B., B.S. UNIV. ADELAIDE 1936 ; Pieter Theron, M.B., CH.B. UNIV. ABERDEEN 1941 ; Charles Kay Warrick, M.B., B.S. UNIV. LOND. 1940 ; Charles Duncan Weir, M.B., CH.B. UNIV. EDIN. 1938 ; George Winchester, M.B., CH.B. UNIV. EDIN. 1937.

Higher Dental Diplomates.—The following candidates, having passed the requisite examinations, were admitted Higher Dental Diplomates : John Spencer Knight, L.D.S., R.C.S. ENG. 1936 ; John Noel Mansbridge, L.D.S.,

R.C.S. EDIN. 1936; Eldred Lennox Manton, L.D.S. UNIV. BRISTOL 1939; Eric Dayton Stanhope, L.D.S., R.C.S. ENG. 1938; Ronald Walker, L.D.S. UNIV. L'POOL 1930.

University of Edinburgh — AT a Graduation Ceremonial held on Friday, 13th December 1946, the following diplomas were conferred :—

The Degree of Doctor of Medicine :—Mervyn Wilfrid Archdall, New Zealand, M.B., CH.B. 1939; Lindsay Francis Brown, New Zealand, M.B., CH.B. 1941 (*Commended for Thesis*) ; Eric Muir Donaldson, Scotland, M.B., CH.B. 1937 (*Commended for Thesis*) ; Jack Greenstein, South Africa, M.B., CH.B. 1925 (*Commended for Thesis*) ; Alexander Finlayson Lang, M.B.E., Scotland, M.B., CH.B. 1941 (*Commended for Thesis*) ; Tormod Macleod, Scotland, M.B., CH.B. 1940 ; Ian Ross Milne, South Africa, M.B., CH.B. 1932 (*Commended for Thesis*) ; Ralph Wilson Gray Ransome-Wallis, D.S.C., England, M.B., CH.B. 1932 ; George Daniel Fraser Steele, Scotland, M.B., CH.B. 1939 (*Highly Commended for Thesis*).

The Degree of Doctor of Science.—Lydia Dorothy Parsons, M.B., CH.B., M.D.

The Degree of Doctor of Philosophy : In the Faculty of Medicine— Muriel Macintosh Johnstone, M.A. ST ANDREWS ; Richard Padley, B.COM. BIRMINGHAM ; Richard Benson Stalbow, B.SC. LOND.

The Degrees of Bachelor of Medicine and Bachelor of Surgery :—Hugh Ian Oliphant Armstrong, B.SC., Scotland ; George Herbert Blair, Scotland ; John Calder, Scotland ; George Richard Duffes, Scotland ; Janet Taylor Young Forrest, Scotland ; Mary Grant Forsyth, England ; George Robert Cecil Dall Gibson, Scotland ; Alexander Charles Jacob, Wales ; Muriel Gwendolene James, England ; David Lewis Kirk, Scotland ; William Harry Lloyd, Wales ; John Morris Loughran, Scotland ; Norman Cranston Low, Scotland ; Alexander MacLennan, Scotland ; Jean Crawford Inglis Melville, Scotland ; Catherine Sands Paterson, Scotland ; James Patrick Payne, Scotland ; John Clark Phemister, Scotland ; Kenneth Robertson, Scotland ; Charles Michael Casterton Smelt, England ; Anne Morag Stewart, Scotland ; Ian Clarke Wilson, Scotland ; John Houston Young, B.A. LOND., Scotland. (*In absentiâ*).

The Polish School of Medicine at Edinburgh—The Degree of Doctor of Medicine :—Aleksander Jacek Baranski, M.D. LWÓW ; Jan Franciszek Majeranowski, M.B., CH.B.

The Degrees of Bachelor of Medicine and Bachelor of Surgery.—Bohdan Adamski, Stefan Dyakowski, Mojżesz Gonszor, Adam Jarosz, Antoni Kepinski, Jerzy Klimczynski, Tadeusz Kłosowski, Jan Kazimierz Koziol, Jan Gabriel Lipski, Władysław Mitus, Zbigniew Prokopowicz, Anna Maria Sokołowska, Mieczysław Szamocki, Zdzislaw Teleszynski, Józef Wilczynski, Hanna Helena Wozniak, Stefan Wozniak, Witold Zaleski, Wladyslaw Żarski.

NEW BOOKS

Squint and Convergence. By N. A. STUTTERHEIM. Pp. 95, with 26 graphs, 15 diagrams and 1 coloured plate. London: H. K. Lewis & Co. Ltd. 1946. Price 15s. net.

Though in recent years some progress has been made in the management of squint hundreds of children still leave the schools of Britain squinting and nearly blind in one eye. Dr Stutterheim's book is therefore very welcome. It is a praise-worthy attempt to point the way to the control of squint. The aim and scope of the book may be indicated by two quotations: " No child, henceforth, should leave the primary school a squinter," and " *School authorities will have to co-operate. . . .* They should understand that squint treatment for the child takes precedence in the curriculum." The nature of squint is discussed in the first twenty pages and the remainder of the book is devoted to treatment. The author rightly stresses the central as against the peripheral or ocular nature of squint, an approach which is by no means new to oculists but worthy of stronger emphasis in practice than circumstances have hitherto permitted. The method of treatment advocated is the re-establishment of binocular and stereoscopic vision by a course of training with prisms. As this requires thirty to sixty hours for each case, not to mention adequate co-operation, the practical difficulties are obvious. The question of amblyopia is hardly touched and the illustrative cases given had all good vision in each eye. The author's style inclines to be elaborate and involved, and the phraseology is sometimes ambiguous so that careful study of each page is required. In spite of such minor faults and although it contains much that is arguable the book is a valuable con-tribution in the right direction and should be in the library of everyone interested in squint. A short bibliography and an index are provided.

Everyday Psychiatry. By JOHN D. CAMPBELL, M.D. Pp. xiv+333. London: J. B. Lippincott & Co. Price 36s. net.

This is an unusual book in that the author—a man of undoubted experience in his speciality—attempts to show general practitioners that many borderline cases can and should be treated by the family doctor. Up to a point he succeeds, but a busy man can only become bewildered in trying to discover the exact category into which his individual case falls. The approach is made through the abnormal per-sonality types, and the author reveals his own enthusiasm when he states that once the physician masters these the quality of clinical medicine will be elevated 25 per cent. " It will be a step forward in medicine equal to the discovery of the sulpha drugs." Such a statement makes no allowance for opportunity and keenness, both of which Commander Campbell has in abundance, but his self-appointed task of blazing a trail will inevitably be an uphill fight no less in the States than here.

There is a service flavour throughout his work which is natural and explains the chance that one in his position has of mass observation, similar in certain respects to that which befalls the medical officer in a Penitentiary ; information from such institutions being freely used. He is familiar with the literature, quotations from which are numerous in the context. The book is written with force and crispness and a careful index will be helpful to those who prefer a more personal approach than is usually found in the text-books.

NEW EDITIONS

Hermaphroditos. By A. P. CAWADIAS, M.D., F.R.C.P. Second Edition. Pp. x+81, with 14 illustrations. London : William Heinemann Ltd. 1946. Price 15s. net.

The author subscribes to the view that the " true " hermaphrodite is non-existent but that there are possible only two classes of intersex, the male and the female. He draws special attention to the milder types of divergence from the normal, not only because they are more common, but also because they are more amenable to treatment. In the present edition the author has re-written the chapter on physio-pathology so as to emphasise the importance of the two different types. He has also recast the clinical chapters to clarify the various forms which may be encountered in practice.

A valuable contribution to a rather obscure field of medicine.

Personal Hygiene Applied. By J. F. WILLIAMS, M.D., SC.D. Eighth Edition, revised. Pp. xx+564, with 156 illustrations. London : W. B. Saunders Co. Ltd. 1946. Price 12s. 6d. net.

This book has been planned for students of health, for physicians, social workers and even for patients. It aims to be scientific and accurate according to the latest information available. It seeks to improve the quality of human life by setting forth the rules of health and relating them to ideals, prejudices, hopes and other sources of human actions. The author takes a very comprehensive view of his subject. "Life is a whole, and hygiene, concerned as it is with living, cannot neglect the whole." The book should appeal to a wide public.

Urological Nursing. By D. M. DAVIS, M.D. Fourth Edition. Pp. vi+212, with 86 figures. London : W. B. Saunders Co. Ltd. 1946. Price 12s.

The special field of urology makes special demands on the nursing staff if the best results are to be obtained, and it is essential that the nurse should have a clear understanding of the problems involved. Professor Davis gives an account of the anatomy, physiology and pathology of the urogenital system ; then describes the nursing technique required and the equipment available. Urological procedures are described in considerable detail and lists of all the equipment required for each are included. This excellent book should serve a useful purpose.

An Atlas of the Commoner Skin Diseases. By H. C. G. SEMON, M.A., D.M., F.R.C.P. Third Edition. Pp. viii+344, with 139 colour plates. Bristol : John Wright & Sons Ltd. 1946. Price 50s. net.

Dr Semon has collected from his patients a series of excellent colour photographs of the dermatoses most commonly seen in general practice. Each illustration is accompanied by a short description of the condition, its differential diagnosis and an outline of the appropriate treatment. The illustrations are remarkably good and give a life-like reproduction of the condition.

This first-class book is one which should be in the possession of every practitioner of medicine.

BOOKS RECEIVED

BROWNE, F. J., D.SC., F.R.C.S.E., F.R.C.O.G. Advice to the Expectant Mother on the Care of her Health and that of her Child. Eighth Edition.
(*E. & S. Livingstone Ltd., Edinburgh*) 9d. net.

BRUNNER, HANS, M.D. Intracranial Complications of Ear, Nose and Throat Infections . . . . (*The Year Book Publishers Inc., Chicago*) $6.75

DAVIS, LOYAL, M.S., M.D., PH.D., D.SC. (HON.). The Principles of Neurological Surgery. Third Edition . . . . (*Henry Kimpton, London*) 37s. 6d. net.

Edinburgh Post-Graduate Lectures in Medicine. Volume Three
(*Published for the Honyman Gillespie Trust by Oliver and Boyd Ltd., Edinburgh*) 15s. net.

Edited by CONYBEARE, Sir JOHN, K.B.E., M.C., D.M., F.R.C.P. Textbook of Medicine. Eighth Edition (*E. & S. Livingstone Ltd., Edinburgh*) 30s. net.

FAIRBROTHER, R. W., M.D., D.SC., F.R.C.P. A Text-Book of Bacteriology. Fifth Edition. . (*Wm. Heinemann (Medical Books) Ltd., London*) 17s. 6d. net.

FLEMMING, CECIL, O.B.E., M.CH., F.R.C.S. Minor Surgery (Heath : Pollard : Davies : Williams). Twenty-third Edition.
(*J. & A. Churchill Ltd., London*) 14s. net.

KARPMAN, BEN, M.D. Case Studies in the Psychopathology of Crime. Volume Two. Cases 6-9. (*Medical Science Press, Washington, D.C., U.S.A.*) —

KEERS, R. Y., M.D., M.R.C.P., F.R.F.P.S., and B. G. RIGDEN, M.R.C.S., L.R.C.P. Pulmonary Tuberculosis. Second Edition.
(*E. & S. Livingstone Ltd., Edinburgh*) 17s. 6d. net.

McDONAGH, J. E. R. The Nature of Disease Up-to-Date.
(*Wm. Heinemann (Medical Books) Ltd., London*) 15s. net.

MACKEE, GEORGE M., M.D., and ANTHONY C. CIPOLLARDO, M.D. X-rays and Radium in the Treatment of Diseases of the Skin. Fourth Edition.
(*Henry Kimpton, London*) 50s. net.

MITCHELL-HEGGS, FRANCIS, T.D., M.B., B.S., F.R.C.S., Major, R.A.M.C. The M.B., B.S. Finals. Third Edition. (*J. & A. Churchill Ltd., London*) 8s. 6d. net.

OPPENHEIMER, JANE M. New Aspects of John and William Hunter.
(*Wm. Heinemann (Medical Books) Ltd., London*) 25s. net.

PERCIVAL, G. H., M.D., PH.D., F.R.C.P.E., D.P.H., A. MURRAY DRENNAN, M.D., F.R.C.P.E., F.R.S.E., and T. C. DODDS, F.I.M.L.T., F.I.B.P., F.R.P.S. Atlas of Histopathology of the Skin. . (*E. & S. Livingstone Ltd., Edinburgh*) 75s. net.

SNOW, WILLIAM, M.D. Principles in Roentgen Study of the Chest.
(*Charles C. Thomas, Springfield, Illinois, U.S.A.*) $10.00

TREISSMAN, H., M.B., B.S., F.R.C.S., D.O.M.S., and E. A. PLAICE. Principles of the Contact Lens . . . . . (*Henry Kimpton, London*) 10s. 6d. net.

URBACH, ERICH, M.D., F.A.C.A., and EDWARD B. LEWINN, B.S., M.D., F.A.C.P. Skin Diseases Nutrition and Metabolism.
(*William Heinemann Ltd., London*) 50s. net.

WALSHE, F. M. R., M.D., D.SC., F.R.C.P., F.R.S., HON. D.SC. On the Contribution of Clinical Study to the Physiology of the Cerebral Motor Cortex. The Victor Horsley Memorial Lecture, 1946.
(*E. & S. Livingstone Ltd., Edinburgh*) 1s. 6d. net.

WESSON, MILEY B., M.D. Urologic Roentgenology. Second Edition.
(*Henry Kimpton, London*) 27s. 6d. net.

WILSON, JAMES V., M.D., M.R.C.P., Major, R.A.M.C. The Pathology of Traumatic Injury . . (*E. & S. Livingstone Ltd., Edinburgh*) 20s. net.

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BOOK REVIEWS